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Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-)

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16. ABSTRACT: The Health and Environmental Effects Profile for Phthalic Acids (o-, m-, p-) was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. p-Phthalic acid has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for p-phthalic acid is 1.4 mg/kg/day for oral exposure. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for o- and m-phthalic acid. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for p-phthalic acid is 1000. Existing data are insufficient to determine an RQ value for o- and m-phthalic acid.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PHTHALIC ACIDS (o-, m-, p-)

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

o-, m- and p-phthalic acid are commonly known as phthalic acid, isophthalic acid and terephthalic acid, respectively. o-Phthalic acid is primarily an unisolated intermediate in the synthesis of phthalic anhydride by air oxidation of o-xylene or napthalene. Quality Chems., Inc., Tyrone, PA, produces o-phthalic acid and six companies manufacture phthalic anhydride (SRI, 1985). In 1984, ~0.98 million pounds of o-phthalic acid were produced as an unisolated intermediate. Phthalic anhydride, the commercial form of o-phthalic acid, is used primarily in plasticizers of which di-(2-ethylhexyl)phthalate is the largest, unsaturated polyester resins and alkyl resins (Bemis et al., 1982). Amoco Chems. Corp., Joliet, IL, is the only manufacturer of m-phthalic acid. m-Phthalic acid is synthesized by sulfur-based oxidation of m-xylene (Bemis et al., 1982). An estimated 101 million pounds of m-phthalic acid were produced in 1980. Of the m-phthalic acid produced in the United States, >50% is used to prepare unsaturated polyester resins. It is also used to make alkyd resins, as a chemical intermediate, as a polyester adhesive, yarn-sizing agent and modifier (Bemis et al., 1982). Technical grade p-phthalic acid is manufactured by the liquid phase air oxidation of p-xylene. Polymer grade p-phthalic acid is produced by purification of the technical grade or hydrolysis of purified dimethyl terephthalate (Bemis et al., 1982). Hercofina, Amoco Chems. Corp., E.I. duPont and Eastman Kodak manufacture p-phthalic acid (SRI, 1985). Of the p-phthalic acid produced, 82% is used in polyethylene terephthalate (polyester) fibers; other uses are in polyethylene terephthalate film and resins and miscellaneous applications including polybutylene terephthalate (CMR, 1983).

In water, o-, m- and p-phthalic acids can be expected to readily dissociate under environmental conditions. Experimental data indicates that reaction of p-phthalic acid with hydroxyl radicals in water is not an important removal mechanism (Dorfman and Adams, 1973). Considering the structural similarities, this may also be true for the o- and m-isomers. Aftring et al. (1981) reported that all the phthalic acid isomers have the potential to degrade under aerobic and anaerobic conditions. o-Phthalic acid has been shown to degrade in river die-away tests by mixed cultures in aquatic sediments (Wylie et al., 1982; Saeger and Tucker, 1973; Taylor and Ribbons, 1983). p-Phthalic acid has been predicted to biodegrade in tests modeling activity in polluted river water and surface waters (Gerike and Fischer, 1979, 1981). o-Phthalic acid has also been shown to degrade under anaerobic conditions (Horowitz et al., 1982; Speece, 1983; Shelton and Tiedje, 1984).

The atmospheric lifespan of o-, m- and p-phthalic acid was estimated to be 1.4 days, based on removal by reaction with hydroxyl radicals (U.S. EPA, 1985a).

In soil, biodegradation is a potential removal mechanism of o-phthalic acid. Inman et al. (1984) observed rapid degradation of o-phthalic acid when incubated with Chalmers silt loam. In addition, several isolated strains of soil bacteria have been shown to degrade o-phthalic acid (Englehart and Wallnofer, 1978; Ribbons and Evans, 1960; Dorney et al., 1985; Eaton and Ribbons, 1982; Perry and Scheld, 1968). Dorney et al. (1985) reported that the dominant removal mechanism for o-phthalic acid applied to soil is degradation or volatilization or both, and that leaching was insignificant.

o-Phthalic acid has been found in aquatic sediments and water and suspended solids samples (U.S. EPA, 1985b). p-Phthalic acid has been detected in polluted river waters (Matsumoto, 1982). Potential emission sources of o-, m- and p-phthalic acids are production, storage and processing facilities, as well as degradation of phthalate plasticizers (Sanbron et al., 1975).

o-Phthalic acid has been identified in precipitation samples from New Hampshire (Likens et al., 1983) and atmospheric fallout near Tokyo, Japan (Matsumoto and Hanya, 1980). o-Phthalic acid has been reported to evolve from coal/refuse combustion (Vick et al., 1978) and tobacco smoking (Peakall, 1975).

o-, m- and p-phthalic acid have apparently leached from packaging materials into a variety of foods (Karasek and Kim, 1975; Foissy, 1979). In addition, exposure to the phthalic acids may result from release from medical products treated with phthalate plasticizers (Karasek and Kim, 1975; U.S. EPA, 1980a).

Little information is available concerning effects of phthalic acid on aquatic organisms. The only toxicity data found was an LC_{50} of 36-40 mg/ℓ for the toad, Bufo bufo japonicus (Nishiuchi, 1980). Studies with two fish species, fathead minnows and channel catfish, exposed to radiolabeled di-2-ethylhexyl phthalate indicated that ~5% of the total accumulated radioactivity was in the form of phthalic acid and its conjugates (Johnson et al., 1977; Mayer, 1976).

Although some studies (Wolkowski-Tyl et al., 1982) suggested incomplete or a slow rate of gastrointestinal absorption in rats, Hoshi and Kuretani (1967) found complete absorption in rats within 24 hours. The difference in strain of rats or vehicles used may account for the discrepancy.

After oral administration of 85 mg/kg ^{14}C-p-phthalic acid in Wistar rats, radioactivity was rapidly and widely distributed and rapidly eliminated from tissues; the greatest accumulation of radioactivity occurred in the liver and kidneys 2 hours after dosing (Hoshi and Kuretani, 1968). There was no trace of radioactivity in any tissue 24-48 hours after dosing.

Reports (Hoshi and Kuretani, 1968; Wolkowski-Tyl et al., 1982) have consistently shown that p-phthalic acid is excreted unmetabolized in the urine. Using thin layer chromatography, Hoshi and Kuretani (1967) failed to observe any metabolites in the urine of female rats given dietary [^{14}C]-p-phthalic acid. No $^{14}CO_2$ was detected in the expired air.

p-Phthalic acid has been found to be completely excreted within 24-48 hours of oral administration (Hoshi and Kuretani, 1967; Wolkowski-Tyl et al., 1982). Hoshi and Kuretani (1967) detected virtually all of the administered label in the urine.

o-Phthalic acid was incompletely absorbed by young male Wistar rats treated by gavage with ^{14}C-o-phthalic acid (Williams and Blanchfield, 1974). At 48 hours after dosing, urinary and fecal excretion accounted for ~20-24% and ~71-78% of the dose, respectively. o-Phthalic acid was rapidly and widely distributed and rapidly eliminated from tissues of rats within 8-24 hours after dosing. Only unchanged o-phthalic acid was found in the urine and feces, although $\leq$0.15% of the dose of radioactivity was found as $^{14}CO_2$ in the expired air. Excretion in the urine and feces was almost complete in the first 24 hours after dosing; very little was excreted over the next 24 hours.

Pertinent data regarding the pharmacokinetics of m-phthalic acid could not be located in the available literature as cited in the Appendix.

In a 2-year study, male and female rats receiving 5% p-phthalic acid in the diet had significantly increased incidences of lesions in the bladder and ureter, which represented a progression ranging through hyperplasia, papilloma, squamous metaplasia to transitional cell tumors or squamous cell carcinoma (Gross, 1974). These lesions occurred at low incidences in rats given 1 or 2%, while none were observed in controls. Increased incidences of transitional cell adenomas and carcinomas were observed in female rats treated for 2 years with p-phthalic acid in the diet at an equivalent dose of 1000 mg/kg/day (CIIT, 1983). The incidence of adenomas was statistically significantly higher than controls. The incidence was not increased in 1000 mg/kg/day males nor in males or females at $\leq$142 mg/kg/day.

p-Phthalic acid was negative for reverse mutations in Salmonella typhimurium with and without metabolic activation (Florin et al., 1980; Zeiger et al., 1982). o-Phthalic acid was negative for chromosome damage in cultured CHO cells (Phillips et al., 1982).

Administration of 2 or 5% dietary p-phthalic acid to breeding pairs of Wistar and CD rats through postweaning, mating and gestation led to decreased viability of male Wistar pups 1 day after birth and of male and female CD pups 21 days after birth (CIIT, 1982). Stillbirths were most prevalent at these two dietary concentrations. Overall, however, neither fertility index nor litter size were adversely affected by treatment. After weaning, dams were continued on their respective diets, as were the pups until dead or sacrificed on day 51. Postweaning, all pups that died had been exposed to the 5% dietary level. The pups exposed to the high concentration also had urinary tract damage and bladder calculi.

Wolkowski-Tyl et al. (1982) reported that rat pups exposed to 5% dietary p-phthalic acid during gestation and lactation or during lactation and up to postnatal day 45 developed calculi only after day 25. The appearance of calculi coincided with the onset of self-feeding. In C3H/He mice perinatally exposed to 0.5% p-phthalic acid, there were no reported adverse effects in either the parental or the F_1 generation (Nagasawa and Fujimoto, 1973).

o-Phthalic acid was not teratogenic or fetotoxic to the offspring of rabbit dams treated orally at 149.5 mg/kg/day (Smith et al., 1965) or mouse dams injected intraperitoneally with up to 400 mg/kg during gestation (Kōhler et al., 1971). No testicular effects were observed in male rats treated by gavage with 2300 mg/kg o-phthalic acid (Cater et al., 1977) or in the diet at 2% for 1 week (Oishi and Hiraga, 1980).

Lifetime administration of 5% dietary p-phthalic acid to Wag/Rij rats led to a greatly accelerated mortality rate relative to controls, evident soon after the onset of treatment (Gross, 1974). Body weights were significantly depressed in females given the 2% concentration, and both relative and absolute liver, kidney and heart weights were decreased in rats receiving the 1 or 2% dietary levels. Increased incidences of uroliths and renal nephropathy were observed only in the rats treated at the 5% dietary concentration; at this level, virtually all rats exhibited urinary tract disorders. Also pronounced at the 5% concentration were nephritis, elevated blood urea levels and hyperplasia progressing to malignant neoplasia of the urinary epithelium.

Female F344 rats fed the dietary equivalent of 1000 mg/kg/day for 18-24 months showed a slight increase in bladder stone formation and transitional cell tumors; these effects were not observed in any rats at $\leq$142 mg/kg/day (CIIT, 1983).

The CIIT (1982) also conducted a subchronic study of dietary p-phthalic administration in Wistar and CD rats. Concentrations used were 0, 0.03, 0.125, 0.5, 2.0 and 5.0%. Rats were sacrificed after 30, 60 or 90 days on the diet, and most adverse effects occurred after the 90-day treatment. These effects, occurring principally in the 5.0% concentration rats, included bladder hyperplasia and distention, bladder calculi, distention of the cecum and colon, and mortality. Starting at the 0.5% level, there were concentration-related trends in urine acidity, the excretion of urinary electrolytes and inhibition in body weight gain. Vogin (1972) observed urolith formation and urinary tract hyperplasia in young rats exposed to a TWA dietary concentration of 3.15% p-phthalic acid for 90 days.

Chin et al. (1981) further demonstrated the susceptibility of young rats to p-phthalic acid intoxication by orally administering the compound for 2 weeks to 28-day-old weanlings. At $\geq$3%, urolith formation was concentration-related, and upon gross necropsy, the affected rats also showed hyperplasia of the bladder and occasional hydronephrosis. The investigators found decreases in urinary sodium, potassium and sulfate in these rats. Microscopic analysis of the urinary tracts of male rats treated with a level of 4% revealed ulceration of the bladder epithelium, inflammation and hyperplasia.

The oral LD_{50}s of o-, m- and p-phthalic acid in rats are 7900, 10,400 and 18,800 mg/kg, respectively (NIOSH, 1985).

An RQ of 1000 was derived based on the reduced survival of pups born to rats treated with p-phthalic acid in the diet in the CIIT (1983) study.

Data were insufficient to calculate RfDs, q_1*s, RQs or F factors for o- and m-phthalic acids.

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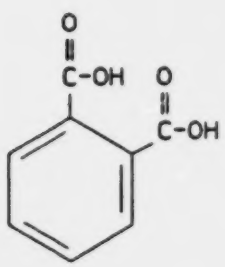
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BODT	Biological oxygen demand, theoretical
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
COD	Chemical oxygen demand
CS	Composite score
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
HPLC	High performance liquid chromatography
K_{oc}	Soil sorption coefficient
KOH	Potassium hydroxide
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
PAH	Polyaromatic hydrocarbon
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
RQ	Reportable quantity
TWA	Time-weighted average
UV	Ultraviolet

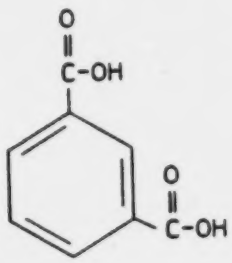
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The three isomers of phthalic acid are o-, m- and p-phthalic acid. o-Phthalic acid is also known as phthalic acid, PA and 1,2-benzenedicarboxylic acid; m-phthalic acid is also called isophthalic acid, IPA and 1,3-benzenedicarboxylic acid; and synonyms of p-phthalic acid are terephthalic acid, TA and 1,4-benzenedicarboxylic acid. The structures, CAS Registry numbers, empirical formula and molecular weight of each compound are as follows:



o-Phthalic Acid



m-Phthalic Acid

p-Phthalic Acid

Molecular weight: 166.13

Empirical formula: $C_8H_6O_4$

CAS Registry number: 88-99-3 - o-phthalic acid

121-91-5 - m-phthalic acid

100-21-0 - p-phthalic acid

1.2. PHYSICAL AND CHEMICAL PROPERTIES

o- and m-Phthalic acid are colorless crystals at room temperature and the p-isomer is a white crystal or powder (Hawley, 1981). Phthalic acids undergo all the reactions characteristic of dicarboxylic acids and can enter into many of the reactions characteristic of the benzene nucleus (Bemis et

al., 1982). The low solubility and high melting point of p-phthalic acid make its reactions somewhat more difficult to carry out than reactions of the other acids (Towle et al., 1968). Selected physical and chemical properties are listed in Table 1-1.

1.3. PRODUCTION DATA

Until World War II, phthalic acid and later, phthalic anhydride were manufactured primarily by liquid-phase oxidation of suitable feedstocks. Currently, phthalic anhydride is manufactured by the catalytic air oxidation of o-xylene or naphthalene (Bemis et al., 1982). Of the phthalic anhydride manufacturing capacity in the United States, 92% is based on o-xylene (SRI, 1985). Phthalic acid is an unisolated intermediate in phthalic anhydride production. o-Phthalic acid typically composes 0.1% (max.) of commercially available phthalic anhydride (Bemis et al., 1982). The following companies and their corresponding products were reported in SRI (1985):

Quality Chem., Inc. (Tyrone, PA)	o-phthalic acid
Bandische Corp. (Kearny, NJ)	phthalic anhydride
Exxon Corp. (Baton Rouge, LA)	phthalic anhydride
Kopper Co., Inc. (Cicero, IL)	phthalic anhydride
Monsanto Co. (Texas City, TX)	phthalic anhydride
Stepan Co. (Bridgeport, NJ)	phthalic anhydride
Tenn-USS Chem. Co. (Pasadena, TX)	phthalic anhydride

In 1984, 0.870 million pounds of phthalic anhydride were produced (USITC, 1985). Therefore, ~0.98 million pounds of o-phthalic acid were produced as an unisolated intermediate.

Amoco Chems. Corp., Joliet, IL, is the only manufacturer of m-phthalic acid (SRI, 1985). m-Phthalic acid is synthesized by sulfur-based oxidation of m-xylene, yielding 98% pure product (Bemis et al., 1982). An estimated 101 million pounds of isophthalate were produced in 1980, based on 86 million pounds of m-xylene produced in 1980 (Ransley, 1984).

TABLE 1-1

Selected Physical and Chemical Properties[a]

Property	o-Phthalic Acid	m-Phthalic Acid	p-Phthalic Acid
Melting point, °C	211	345-348[b]	427
Boiling point °C	decomposes	sublimes	sublimes
Vapor pressure at 20°C	NA	<0.075 mm Hg	0.15 mm Hg
Water solubility at 25°C (mg/ℓ)	7000	130	19
Log K_{ow}	0.73	1.66	2.00
pK_1	2.95	3.48	3.51
pK_2	5.41	4.49	4.82
Specific gravity	1.593 at 4°C	1.507 at 20°C	1.510 at 20°C
Minimum explosive concentration in air (mg/ℓ)	NA	50	35

[a]Sources: Towle et al., 1968; Bemis et al., 1982; Hawley, 1981; Hansch and Leo, 1985; Weber et al., 1981

[b]closed tube

NA = Not available

Nearly all the technical grade p-phthalic acid is produced by liquid-phase air oxidation of p-xylene. The most popular process is the Amoco technology process, which yields 90 mol % p-phthalic acid. Polymer grade p-phthalic acid is produced by purifying the technical grade product (Bemis et al., 1982). In another commercially applied process, polymer grade p-phthalic acid is formed by the hydrolysis of purified dimethyl terephthalate (Bemis et al., 1982). Primary manufacturers listed by SRI (1985) are as follows:

Hercofina	Wilmington, NC	polymer grade
Amoco Chems. Corp.	Charleston, SC	technical and
	Decatur, AL	polymer grades
EI duPont	Old Hickory, TN	technical grade
	Wilmington, NC	technical grade
Eastman Kodak Co.	Columbia, SC	technical grade
	Kingsport, TN	technical grade

Dimethyl terephthalate and polymer grade p-phthalic acid are used interchangeably (Bemis et al., 1982). Thus, in 1984, 5.912 million pounds of p-phthalic acid/dimethyl terephthalate were manufactured, but individual production figures were not reported (USITC, 1985).

1.4. USE DATA

Di-(2-ethylhexyl)phthalate (DEHP), the largest volume plasticizer, is a main consumer of o-phthalic acid. Phthalic anhydride, principally the commercial form of o-phthalic acid, is used mainly in plasticizers, unsaturated polyester resins and alkyd resins. A significant proportion of the remaining phthalic anhydride is used in the manufacture of dyes (i.e., 2-chloroanthraquinone) (Bemis et al., 1982).

More than 50% of the isophthalic acid produced in the United States is used to prepare unsaturated polyester resins called isopolyesters, while the second largest use is in alkyd resins. Other applications are as a chemical

intermediate, polyester adhesive, yarn-sizing agent for polyethylene terephthalate fibers and as a modifier for polyethylene terephthalate fibers and films, isophthalate esters and isophthaloyl chloride (Bemis et al., 1982).

The use pattern of dimethyl terephthalate/p-phthalic acid is as follows (CMR, 1983):

Polyethylene terephthalate (polyester) fibers	82%
Polyethylene terephthalate film	8%
Polyethylene terephthalate resin	6%
Miscellaneous (including polybutylene terephthalate)	4%

1.5. SUMMARY

o-, m- and p-phthalic acid are commonly known as phthalic acid, isophthalic acid and terephthalic acid, respectively. o-Phthalic acid is primarily an unisolated intermediate in the synthesis of phthalic anhydride by air oxidation of o-xylene or napthalene. Quality Chems., Inc., Tyrone, PA, produces o-phthalic acid and six companies manufacture phthalic anhydride (SRI, 1985). In 1984, ~0.98 million pounds of o-phthalic acid were produced as an unisolated intermediate. Di-(2-ethylhexyl)phthalate is a primary consumer of o-phthalic acid; phthalic anhydride is used principally in plasticizers, unsaturated polyester resins and alkyd resins (Bemis et al., 1982). Amoco Chems. Corp., Joliet, IL, is the only manufacturer of m-phthalic acid. m-Phthalic acid is synthesized by sulfur-based oxidation of m-xylene (Bemis et al., 1982). An estimated 101 million pounds of m-phthalic acid were produced in 1980. Of the m-phthalic acid produced in the United States, >50% is used to prepare unsaturated polyester resins. It is also used to make alkyd resins, as a chemical intermediate, as a polyester adhesive, yarn-sizing agent and modifier (Bemis et al., 1982).

Technical grade p-phthalic acid is manufactured by the liquid phase air oxidation of p-xylene. Polymer grade p-phthalic acid is produced by purification of the technical grade or hydrolysis of purified dimethyl terephthalate (Bemis et al., 1982). Hercofina, Amoco Chems. Corp., E.I. duPont and Eastman Kodak manufacture p-phthalic acid (SRI, 1985). Of the p-phthalic acid produced, 82% is used in polyethylene terephthalate (polyester) fibers; other uses are in polyethylene terephthalate film and resins and miscellaneous applications including polybutylene terephthalate (CMR, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The dissociation constants of o-, m- and p-phthalic acid listed in Table 1-1 indicate that these acids should readily dissociate to their corresponding ions in water under environmental conditions (pH 6-8).

2.1.1. Hydrolysis. Jaber et al. (1984) stated that there are no hydrolyzable functional groups on any of the phthalic acid isomers.

2.1.2. Oxidation. Pertinent data regarding the oxidation of the o- and m-isomers of phthalic acid in water could not be located in the available literature as cited in the Appendix. The reaction rate constant of hydroxyl radicals with p-phthalic acid was experimentally determined to be 1.92×10^{9} M^{-1} sec^{-1} (Dorfman and Adams, 1973). Assuming a hydroxyl radical concentration of 10^{-17} M in water, the half-life of p-phthalic acid in water that is due to this reaction has been calculated to be 1.1 years.

2.1.3. Photolysis. Jaber et al. (1984) stated that photolysis is not an environmentally relevant reaction mechanism for o-, m- and p-phthalic acid in water.

2.1.4. Microbial Degradation. Aftring et al. (1981) reported that o-, m- and p-phthalic acids have the potential to degrade under both aerobic and anaerobic conditions. Wylie et al. (1982) observed 66-92% degradation of o-phthalic acid in three replicate samples of Missouri River water taken at four different times (total of 12 samples tested). o-Phthalic acid added to these samples were not a major carbon source for the microbiota. In another river die-away study, Saeger and Tucker (1973) determined that a 12.5 ppm o-phthalic acid sample had a degradation half-life of 1.5 weeks in unacclimated Mississippi River water. Aerobic degradation of o-phthalic acid has also been studied by Taylor and Ribbons (1983) by a mixed culture in aquatic

sediment. Gerike and Fischer (1979, 1981) studied the microbial degradation of p-phthalic acid in tests modeling polluted river water (AFNOR T90-302 test) and surface waters (Sturm, modified OECD screening and closed bottle tests). Results of these tests are presented in Table 2-1.

Kitano (1978) determined that all the phthalic acid isomers were biodegradable by the MITI test. Kawasaki (1980) categorized o-phthalic acid as degradable by this test and Sasaki (1978) also reported that >30% of 100 ppm m- and p-phthalic acid samples were degraded in 2 weeks by activated sludge at pH 7 and 25°C. In contrast, Gerike and Fischer (1979) reported no degradation of p-phthalic acid by the MITI test. In a semi-continuous activated sludge system, 99+% of o-phthalic acid samples added at a rate of 50-250 mg/24 hours was biodegraded (Saeger and Tucker, 1976). Saeger and Tucker (1976) stated that the results of their river die-away and acclimated sludge tests, together with the rapid acclimation observed in these systems, indicated that o-phthalic acid would readily degrade in mixed microbial populations. Zahn and Wellens (1980) reported >90% degradation in 4 days of an o-phthalic acid sample at a concentration equal to 100 mg/ℓ COD by nonadapted activated sludge. Clearly definable degradation began 1 day following the start of the experiment and proceeded at a rate of 27% COD reduction per day. Other activated sludge systems have also been shown to degrade o-phthalic acid (Pitter, 1976; Heukelekian and Rand, 1955).

Horowitz et al. (1982) determined that o-phthalic acid undergoes anaerobic degradation in both freshwater lake sediment and municipal sludge. Speece (1983) and Shelton and Tiedje (1984) also observed biodegradation of o-phthalic acid under anaerobic conditions.

2.1.5. Volatilization. Pertinent data regarding volatilization of o-, m- or p-phthalic acid from water could not be located in the available

TABLE 2-1

Results of Biodegradation Tests in p-Phthalic Acid*

Test	% Doc Removed	% CO_2 Evolved	% BODT
AFNOR T90-302 Test (28-42 days)	66	NA	NA
Sturm Test (28 days)	91	72	NA
Modified OECD Screening Test (19 days)	82	NA	NA
Closed Bottle Test (30 days)	NA	NA	112

*Source: Gerike and Fischer, 1979, 1981

NA = Not applicable

literature as cited in the Appendix. The dissociation of these compounds in water suggests that volatilization will not occur. Further indication that the phthalic acid isomers will not evaporate is suggested by the Henry's Law Constant of $\leq 9.55 \times 10^{-13}$ $m^3 \cdot atm/mol$ estimated by the structure-based bond and group contribution methods of Hine and Mookerjee (1975).

2.1.6. Bioaccumulation. Pertinent data regarding bioaccumulation of the phthalic acid isomers in water could not be located in the available literature as cited in the Appendix; however, BCFs have been estimated for each isomer and are listed in Table 2-2. These data suggest that bioaccumulation of the o- and m-isomers would not be significant, but there could be a slight potential for bioaccumulation of the p-isomer.

2.1.7. Adsorption. Pertinent data on the adsorption of o-, m- or p-phthalic acid to suspended particulates or sediments in water could not be located in the available literature as cited in the Appendix.

2.2. AIR

No experimental data on the environmental fate and transport of phthalic acid isomers in the atmosphere were located; however, the hydroxyl reaction rate constant was estimated to be 5.37×10^{-13} $cm^3/molecule \cdot sec$ for the phthalic acid isomers at 25°C (U.S. EPA, 1985a). Assuming an ambient atmospheric hydroxyl radical concentration of 8.0×10^5 $molecule/cm^3$, the lifespan of the phthalic acid isomers has been calculated to be 1.4 days (U.S. EPA, 1985a).

2.3. SOIL

2.3.1. Hydrolysis. The phthalic acid isomers have no hydrolyzable substituents (Jaber et al., 1984).

2.3.2. Oxidation. Pertinent data regarding the oxidation of the phthalic acid isomers in soil could not be located in the available literature as cited in the Appendix.

TABLE 2-2

BCFs of the Phthalic Acid Isomers*

Equations	BCF		
	o-	m-	p-
Log BCF = 0.76 log K_{OW} - 0.23	2	0.9	19
Log BCF = 2.791-0.564 log S	4	40	117

*Source: Lyman et al., 1982

2.3.3. Photolysis. Experimental data on the photolysis of the phthalic acid isomers on soil surfaces were not located; however, the UV absorption spectra for o-, m- and p-phthalic acids reveal absorption at wavelengths >290 nm, indicating a potential for photolysis (Ribbons and Evans, 1960; Sadtler, n.d.).

2.3.4. Microbial Degradation. Inman et al. (1984) studied the biodegradation of o-phthalic acid incubated with Chalmers silt loam. Rapid degradation was observed and 100% decomposition was measured after 53 days. Isolated Nocardia sp. and Pseudomonas sp. rapidly oxidized o-phthalic acid to protocatechuic acid by 3,4-dioxygenative ring cleavage (Englehart and Wallnofer, 1978; Ribbons and Evans, 1960). In addition, Bacillus sp. and Pseudomonas testosteroni have been shown to metabolize o-phthalic acid to benzoic acid (Dorney et al., 1985). Other studies have shown that o-phthalic acid can be reduced by the soil bacteria, Micrococcus sp. strain 128 and Arthrobactor sp. (Eaton and Ribbons, 1982; Perry and Scheld, 1968).

2.3.5. Volatilization. Dorney et al. (1985) applied 0.6, 6.0, 60.0 and 600.0 ppm (dry weight) radiolabeled o-phthalic acid to the top soil of corn/wheat and soybean/fescue pots containing Norfolk sandy loam. Over an 80-day period, 94.3% was lost through volatilization or decomposition.

Data regarding the volatilization of m- and p-phthalic acid could not be located in the available literature as cited in the Appendix.

2.3.6. Adsorption. Dorney et al. (1985) observed that an average of 0.02% of o-phthalic acid applied to soils were leached to the bottom soil layer compared with an average of 5.7% recovered from plants and top soil. In addition, slight mobility for all the phthalic acid isomers is indicated by a K_{oc} value of 3390 estimated by the structural analysis method of Sabljic (1984).

2.4. SUMMARY

In water, o-, m- and p-phthalic acids can be expected to readily dissociate under environmental conditions. Experimental data indicate that reaction of p-phthalic acid with hydroxyl radicals in water is not an important removal mechanism (Dorfman and Adams, 1973). Considering the structural similarities, this may also be true for the o- and m-isomers. Aftring et al. (1981) reported that all the phthalic acid isomers have the potential to degrade under aerobic and anaerobic conditions. o-Phthalic acid has been shown to degrade in river die-away tests by mixed cultures in aquatic sediments (Wylie et al., 1982; Saeger and Tucker, 1973; Taylor and Ribbons, 1983). p-Phthalic acid has been reported to biodegrade in tests modeling activity in polluted river water and surface waters (Gerike and Fischer, 1979, 1981). o-Phthalic acid has also been shown to degrade under anaerobic conditions (Horowitz et al., 1982; Speece, 1983; Shelton and Tiedje, 1984).

The atmospheric lifespan of o-, m- and p-phthalic acid was estimated to be 1.4 days, based on removal by reaction with hydroxyl radicals (U.S. EPA, 1985a).

In soil, biodegradation is a potential removal mechanism of o-phthalic acid. Inman et al. (1984) observed rapid degradation of o-phthalic acid when incubated with Chalmers silt loam. In addition, several isolated strains of soil bacteria have been shown to degrade o-phthalic acid (Englehart and Wallnofer, 1978; Ribbons and Evans, 1960; Dorney et al., 1985; Eaton and Ribbons, 1982; Perry and Scheld, 1968). Dorney et al. (1985) reported that the dominant removal mechanism for o-phthalic acid applied to soil is degradation or volatilization or both, and that leaching was insignificant.

3. EXPOSURE

3.1. WATER

Monitoring data for o-phthalic acid reported in the U.S. EPA STORET data base is presented in Table 3-1; no information was available on m- or p-phthalic acid. p-Phthalic acid has been identified in polluted river waters in Japan at levels ranging from 1.1-3.4 µg/ℓ (Matsumoto, 1982). Water samples obtained from remote (unpolluted) rivers contained no detectable p-phthalic acid. o-Phthalic acid at concentrations >1 mg/ℓ has been measured in primary effluent discharged from a municipal waste treatment facility (U.S. EPA, 1975). o-Phthalic acid wastes have also been found in wastewaters from the paint and varnish industries and alkyl resin plants (U.S. EPA, 1980a). o-Phthalic acid, m- and p-phthalic acid may be emitted to ambient waters from production, storage and processing facilities. In addition, o-phthalic acid is a primary degradation product of dioctyl phthalate in water and could possibly be a degradation product of other phthalate plasticizers (Sanbron et al., 1975).

3.2. DERMAL

Pertinent data regarding dermal exposure to o-, m- and p-phthalic acid could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Kawamura et al. (1985) measured an average of 0.22 µM o-phthalic acid in 50 mℓ (36.5 µg/ℓ) of rainwater, 3.97 µM in 1 mℓ (59 µg/ℓ) of fog and 0.85 µM in 2 mℓ (141 µg/ℓ) of mist all collected in the Los Angeles area. The authors concluded that phthalic acid may have formed by the hydrolysis of phthalates or the photooxidation of naphthalenes, since naphthalenes were detected as major PAHs in the rainwater samples.

TABLE 3-1

Monitoring Data for o-Phthalic Acid*

	Sediment (µg/kg dry weight)	Water and Suspended Solids (µg/ℓ)
Number of Samples	3	5
Maximum Concentration	6500	1000
Minimum Concentration	1500	1.0
Mean Concentration	4333	422.2

*Source: U.S. EPA, 1985b

Matsumoto and Hanya (1980) qualitatively analyzed o-phthalic acid in the atmospheric fallout near Tokyo, Japan. Vick et al. (1978) detected o-phthalic acid in the vapors and ashes from combustion of the combination coal/refuse. o-Phthalic acid has also been detected in tobacco at levels of 0.35 mg/100 g of tobacco smoked (Peakall, 1975).

Ambient monitoring data on m- and p-phthalic acid could not be located in the available literature as cited in the Appendix.

Vick et al. (1978) suggested that stationary sources, such as stacks, may contribute significantly to the level of o-phthalic acid in the environment. Potential sources of emissions of all phthalic acid isomers could be production and processing facilities.

3.4. FOOD

The isomeric phthalic acids have been detected in cooking fat, vegetables, fruits, fish, meat, milk, butter and cheese, which is apparently due to migration from polymeric packaging materials (Karasek and Kim, 1975; Foissy, 1979). o-Phthalic acid has also been found in raspberries (Peakall, 1975).

3.5. OTHER RELEVANT INFORMATION

Release of phthalic acids from plastic medical devices (blood bags, plastic tubing, catheters, etc.) may occur since these materials have been treated with phthalate plasticizers; however, no specific data on release were available (U.S. EPA, 1980a; Karasek and Kim, 1975).

3.6. SUMMARY

o-Phthalic acid has been found in aquatic sediments and water and suspended solids samples (U.S. EPA, 1985b). p-Phthalic acid has been detected in polluted river waters (Matsumoto, 1982). Potential emission sources of

o-, m- and p-phthalic acids are production, storage and processing facilities, as well as degradation of phthalate plasticizers (Sanbron et al., 1975).

o-Phthalic acid has been identified in precipitation samples and atmospheric fallout near Tokyo, Japan (Matsumoto and Hanya, 1980). o-Phthalic acid has been reported to evolve from coal/refuse combustion (Vick et al., 1978) and tobacco smoking (Peakall, 1975).

o-, m- and p-phthalic acid have apparently leached from packaging materials into a variety of foods (Karasek and Kim, 1975; Foissy, 1979). In addition, exposure to the phthalic acids may result from release from medical products treated with phthalate plasticizers (Karasek and Kim, 1975; U.S. EPA, 1980a).

4. PHARMACOKINETICS

4.1. ABSORPTION

Hoshi and Kuretani (1967) studied the extent, rate and site of absorption of p-phthalic acid from the gastrointestinal tract. Groups of five adult female Wistar rats were treated by gavage with 85 mg/kg [^{14}C-carboxyl] p-phthalic acid suspended in sodium carboxymethyl cellulose. Groups were sacrificed at 2, 4, 6, 8, 24 and 48 hours postadministration, at which times urine and fecal samples were also taken. At sacrifice, the gastrointestinal tract was divided into esophagus and stomach, small intestine, cecum and large intestine, and radiation was counted by liquid scintillation. Amounts of $^{14}CO_2$ in the expired air were measured for 24 hours. Analysis of the levels of radioactivity remaining in the gastrointestinal tract revealed that 36.2, 63.7, 74.8 and 86.2% of the dose disappeared in 2, 4, 6 and 8 hours, respectively. No radioactivity was detected at 24 hours. At 8 hours after dosing, urine accounted for 82.1% of the administered radioactivity and the feces 0%. By 24 hours, excretion was virtually complete, with the urine accounting for 93.5% and the feces 3.3%. There was essentially no radioactivity detected in expired air. The authors calculated that >70% of the administered dose was absorbed from the upper (stomach and small intestine) portions of the gastrointestinal tract and >22% was absorbed from the cecum and large intestine.

Wolkowski-Tyl et al. (1982) found different plasma clearance profiles of ^{14}C-p-phthalic acid in female F344 rats dosed intravenously or by gavage (Section 4.4.). The longer half-life following oral dosing suggested that gastrointestinal absorption was rate limiting. Wolkylski-Tyl et al. (1982), like Hoshi and Kuretani (1967), used sodium carboxymethyl cellulose as the vehicle for oral dosing; however, Wolkowski-Tyl et al. (1982) did not measure urinary and fecal excretion.

Williams and Blanchfield (1974) studied the pharmacokinetics of o-phthalic acid in young male Wistar rats. The rats were given a single dose of ^{14}C-o-phthalic acid (labeled in Carbon atom 7) in water by gavage at 0.4, 4 or 40 mg/kg. At 48 hours after dosing, urinary excretion accounted for 20.6-24.4% of the dose and fecal excretion for 71.4-78.4%. Expired $^{14}CO_2$ at 24 hours after oral doses of 3.3 and 40 mg/kg of ^{14}C-o-phthalic acid accounted for only 0.11 and 0.15% of the dose, respectively. $^{14}CO_2$ was not detected in subsequent 24-hour samples.

Pertinent data regarding the absorption of m-phthalic acid could not be located in the available literature as cited in the Appendix.

4.2. DISTRIBUTION

Six groups of five female Wistar rats were orally dosed with 85 mg/kg [^{14}C-carboxyl] p-phthalic acid in 0.5% sodium carboxymethyl cellulose (Hoshi and Kuretani, 1968) and were sacrificed after 2, 4, 6, 8, 24 and 48 hours. Nineteen organs and tissues were analyzed for radioactivity. Radioactivity was rapidly and widely distributed and rapidly eliminated from the tissues. Peak levels were reached within 2 hours for all tissues except the brain. The level in the brain rose slowly until 8 hours after dosing, then declined to 0 at 48 hours. Highest levels of radioactivity were found in plasma, kidney and liver; at 2 hours after dosing, levels in these tissues were ~10 µg/mℓ, 58 and 31 µg/g, respectively. Levels in other tissues at 2 hours were $\leq$6 µg/g. The levels in most tissues declined to 0 in 24 hours and in kidney, liver, brain and skin in 48 hours. Tissue elimination curves (except brain), beginning at 2 hours after dosing, were linear and nearly parallel to the plasma elimination curves. Elimination half-lives for tissues were 1.2-3.3 hours; the plasma elimination half-life was 2.43 hours.

Hoshi and Kuretani (1968) also studied tissue distribution after feeding 15 female Wistar rats a diet containing 0.5% [^{14}C-carboxyl] p-phthalic acid. The 15 rats were divided into three groups: Group A was sacrificed immediately after 1 day on the diet; Group B was killed immediately after a 3-day feeding; and Group C was killed 1 day after the 3-day feeding. The distribution pattern for Groups A and B, regardless of duration, was similar to that of the single dosed group. In all tissues except the skin (1.2 µg/g), radioactivity levels for Group C rats were negligible ($\leq$0.31 µg/g).

Wolkowski-Tyl et al. (1982) administered 60 µCi/rat of [^{14}C]-p-phthalic acid by gavage to gravid F344 rats on gestation day 20. At specified times (from 45 minutes to 12 hours later), the rats were sacrificed, and the maternal serum, liver, kidneys, placentae and urine were collected. Concentrations of radioactivity were higher in the urine than in the other tissues of the dams at all time points. The levels in the tissues declined rapidly, and the estimated half-life in serum was ~1.3 hours. Fetal tissues examined included the livers, kidneys, bladder and serum. After a 1.5-hour delay, the levels of radioactivity in the fetal bladder were higher than in the other organs at all sacrifice times. The estimated half-life in the fetal bladder was 3 hours. Although p-phthalic acid crossed the placental barrier, concentrations of radioactivity in the maternal tissues were 2-3 times higher than in the fetal tissues.

Williams and Blanchfield (1974) studied the distribution of o-phthalic acid in rats. Male Wistar rats were treated by gavage with 4 mg/kg ^{14}C-o-phthalic acid in water. The rats were killed at 4, 8 or 24 hours after dosing. Measurable levels of radioactivity were found in the spleen, kidney, liver, adipose-tissue, skeletal muscle, lungs, testes, heart and

skin at 4 hours. Levels of radioactivity declined to zero in the liver at 8 hours and in all other tissues at 24 hours. No radioactivity was found in the brain at any sampling time.

Pertinent data regarding the distribution of m-phthalic acid could not be located in available literature as cited in the Appendix.

4.3. METABOLISM

Hoshi and Kuretani (1968) and Wolkowski-Tyl et al. (1982) found that p-phthalic acid is excreted unchanged in the urine and feces. In an attempt to specifically identify urinary metabolites, Hoshi and Kuretani (1967) fed female rats a diet supplemented with 0.5% [^{14}C-carboxy] p-phthalic acid and collected urine fractions 6-8 hours after initiation of the diet. Analysis of thin layer chromatography plates by both spray reagents and autoradiography revealed only unmetabolized p-phthalic acid. No $^{14}CO_2$ was detected in the expired air.

Williams and Blanchfield (1974) found only unchanged o-phthalic acid in the urine and feces of rats treated by gavage with 3.3 or 40 mg/kg ^{14}C-o-phthalic acid (labeled at Carbon atom 7). Small amounts of $^{14}CO_2$ (0.11 and 0.15% of the respective doses) were detected, but only in the first 24 hours after dosing.

Pertinent data regarding the metabolism of m-phthalic acid could not be located in the available literature as cited in the Appendix.

4.4. EXCRETION

As discussed in Section 4.1., Hoshi and Kuretani (1967) orally dosed female rats with radiolabeled p-phthalic acid. Excretion of unmetabolized compound was virtually complete 24 hours after dosing, at which time, 93.5% of the administered radioactivity was found in the urine and 3.3% in the feces. No measurable carbon dioxide was found in the expired air.

In a study by Wolkowski-Tyl et al. (1982), a single intravenous bolus of [^{14}C]-p-phthalic acid resulted in a plasma elimination terminal phase half-life of 1.2 hours and complete urinary recovery of label after 8 hours. The plasma clearance was essentially the same as the renal clearance. After oral dosing, plasma levels of radioactivity slowly declined up to 400 minutes after dosing. The authors suggested that absorption from the gastrointestinal tract was rate-limiting. In rats orally dosed with 0.4-40 mg/kg radiolabeled o-phthalic acid, ~23% of the administered label was recovered in the urine, 72% in the feces and $\leq$0.15% as $^{14}CO_2$ 24 hours after dosing (Williams and Blanchfield, 1974). Very little was excreted over the next 24 hours.

Pertinent data regarding the excretion of m-phthalic acid could not be located in the available literature as cited in the Appendix.

4.5. SUMMARY

Hoshi and Kuretani (1967) found complete absorption in rats within 24 hours. The difference in strain of rats or vehicles used may account for the discrepancy. After oral administration of 85 mg/kg ^{14}C-p-phthalic acid in Wistar rats, radioactivity was rapidly and widely distributed and rapidly eliminated from tissues; the greatest accumulation of radioactivity occurred in the liver and kidneys 2 hours after dosing (Hoshi and Kuretani, 1968). There was no trace of radioactivity in any tissue 24-48 hours after dosing. Examination of the fetuses of 20-day gravid rats that were treated orally with ^{14}C-p-phthalic acid revealed radioactivity in the bladder, kidney, liver, serum and amniotic fluid. Levels in the fetal bladder were higher than in the other fetal tissues. The levels of radioactivity in the fetal tissues were 2-3 times lower than in the maternal tissues.

Reports (Hoshi and Kuretani, 1968; Wolkowski-Tyl et al., 1982) have consistently shown that p-phthalic acid is excreted unmetabolized in the urine. Using thin-layer chromatography, Hoshi and Kuretani (1967) failed to observe any metabolites in the urine of female rats given dietary [^{14}C]-p-phthalic acid. No $^{14}CO_2$ was detected in the expired air.

p-Phthalic acid has been found to be completely excreted within 24-48 hours of oral administration (Hoshi and Kuretani, 1967; Wolkowski-Tyl et al., 1982). Hoshi and Kuretani (1967) detected virtually all of the administered label in the urine.

o-Phthalic acid was incompletely absorbed by young male Wistar rats treated by gavage with ^{14}C-o-phthalic acid (Williams and Blanchfield, 1974). At 48 hours after dosing, urinary and fecal excretion accounted for ~20-24% and ~71-78% of the dose, respectively. o-Phthalic acid was rapidly and widely distributed and rapidly eliminated from tissues of rats within 8-24 hours after dosing. Only unchanged o-phthalic acid was found in the urine and feces, although $\leq$0.15% of the dose of radioactivity was found as $^{14}CO_2$ in the expired air. Excretion in the urine and feces was almost complete in the first 24 hours after dosing; very little was excreted over the next 24 hours.

Pertinent data regarding the pharmacokinetics of m-phthalic acid could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

In a 2-year carcinogenicity bioassay, groups of 50 male and 50 female Wag/Rij (Wistar) rats were administered p-phthalic acid (97.3% pure) at dietary concentrations of 0, 1, 2 or 5% (Gross, 1974). All rats were examined daily, weighed weekly for the first 3 months and biweekly thereafter. Upon terminal sacrifice, at least 13 tissues were examined histologically. Blood was taken at the time of sacrifice for hematological and urea concentration analyses. Histological analysis of nonautolyzed tissues from rats that died or were killed when moribund was also performed.

The 5% dietary concentration greatly accelerated mortality rates in both sexes, whereas survival was not adversely affected by administration of 1 or 2% p-phthalic acid. The increased mortality of the high-dose group was due to formation of stones in the urinary tract (Section 5.5.). As shown in Table 5-1, both male and female rats fed 5% dietary p-phthalic acid had significantly ($p<0.001$) greater incidences of bladder and ureteral hyperplastic lesions and tumors. In both sexes, the Cochran-Armitage test for dose-related trend was also statistically significant ($p<0.001$). Gross (1974) delineated a series of progressive stages ranging through hyperplasia, papilloma, squamous metaplasia to both transitional cell tumors and squamous cell carcinoma. He was, however, unclear about the nature of the incidence data, stating that it represented "the frequency of occurrence of changes from hyperplasia to tumor." The hyperplastic and neoplastic changes in the bladder epithelium were secondary to the presence of stones.

CIIT (1983) conducted a lifetime bioassay of dietary p-phthalic acid in male and female F344 rats. Dietary p-phthalic acid was administered at equivalent doses of 0, 20, 142 and 1000 mg/kg/day for 2 years. Groups of rats were sacrificed at interim time periods of 6, 12, 18 or 24 months.

TABLE 5-1

Incidences of Bladder and Ureteral Neoplasms
in Male and Female Wag/Rij (Wistar) Rats Given 97.3%
Dietary p-Phthalic Acid for 2 Years[a,b]

Sex	Concentration (ppm)	Tumor Incidence[c] (p value)
M	0	0/45 (p<0.001)[d]
	10,000	1/43
	20,000	1/48
	50,000	21/37 (p<0.001)[e]
F	0	0/46 (p<0.001)[d]
	10,000	0/48
	20,000	2/47
	50,000	21/34 (p<0.001)[e]

QUALITY OF EVIDENCE

Strengths of Study: Sufficient number of rats at each of three concentrations. Equal numbers of matched controls. Relevant exposure route and duration of exposure. Concentration-response relationship established.

Weakness of Study: The incidence of hyperplasia, benign tumors and malignant tumors alone were not provided.

Overall Adequacy: Adequate

[a]Source: Gross, 1974

[b]Initially: 50 rats/group

[c]Incidence data reflect frequency of occurrence of changes ranging through hyperplasia, papillomas, squamous metaplasia to both transitional cell-tumors and squamous cell carcinoma.

[d]Significance level by Cochran-Armitage test for dose-related trend performed at SRC

[e]Significance level for individual comparison by Fisher Exact test performed at SRC.

The initial study evaluated only the control and high-dose animals histologically at the final sacrifice. Slides for all dose groups were subsequently sent for an independent evaluation. At the 24-month sacrifice, the two laboratories reported that the incidence of transitional cell adenoma in the bladders of 1000 mg/kg/day females was higher (15/79 or 10/73) than in controls (1/83 or 1/71), but that no other group showed this tumor type. The difference in the denominators reflects that all of the slides were not successfully delivered. Fisher Exact tests performed at SRC revealed that the incidences determined by either laboratory are significantly higher than controls ($p \leq 0.005$). Transitional cell carcinomas were also observed in 1000 mg/kg/day females only (2/79 or 1/73).

Body weight and food consumption were monitored on a weekly basis and dietary concentration adjusted accordingly to maintain the targeted doses. Initially, 126 animals/sex/dose were included in the study. It is not clear how many animals were initially scheduled for the interim sacrifices. It appears that 5 animals/group were scheduled for 6 and 12 months with an additional 20 scheduled for 18 months. The number of bladders examined at the terminal sacrifice were 83 for female controls, 87 for male controls, 79 for high-dose females and 82 for high-dose males. These tissues also included animals that died between the 18-month and 24-month sacrifice.

In addition to the tumors, high-dose females were the only group to show urinary bladder stones, which appeared in 6/49 animals at the terminal sacrifice and 5/37 animals dying during the final study period. Uterine masses occurred in 17% of the control animals, 22% of the low-dose animals, 24% of the mid-dose animals and 25% of the high-dose animals. Many of the masses were subsequently diagnosed as adenocarcinomas. In addition, there

was an abnormally high incidence of eye lesions. The report suggests that the only unusual circumstance of the study was a study room light cycle dysfunction of unknown duration.

Bladder lesions also occurred in females in the high-dose group at the 18-month sacrifice, but not in males or other dose groups even at the terminal sacrifice. Other signs of toxicity included lower rate of weight gain in high-dose males and females. Reduction in absolute organ weights were seen for lungs, heart, liver and kidney in high-dose males and heart and kidney for females; however, the only difference in organ-to-body weight ratio was a reduction for relative brain weight in high-dose females.

Nagasawa and Fujimoto (1973) investigated the effects of dietary p-phthalic acid administration on mammary tumorigenesis in female C34/He mice. Thirty-one mice received a commercial diet containing 0.5% p-phthalic acid and 116 controls were fed the commercial diet only, beginning immediately postweaning and continuing until the mice died or developed a tumor. Mice were examined weekly from months 4-16 for palpable masses. From the 6-16th month, the compound significantly decreased the rate of spontaneous mammary tumorigenesis. Inhibition of the rate of tumor formation was especially pronounced from months 10-13. Additionally, the intratumor injection of p-phthalic acid had no effect on the development of Ehrlich solid carcinomas.

Pertinent data regarding the carcinogenicity of o- or m-phthalic acid could not be located in the available literature as cited in the Appendix.

5.2. MUTAGENICITY

Experiments involving mutagenic testing of the phthalic acids are summarized in Table 5-2. p-Phthalic acid has been found not to cause reverse mutations in Salmonella typhimurium, with or without metabolic activation

TABLE 5-2

Mutagenicity Testing of Phthalic Acids

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100 TA1535, TA1537	p-phthalic acid in DMSO	spot test	3 µmol/plate	±S-9	-	Quantitative test not done	Florin et al., 1980
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	p-phthalic acid in DMSO/98%	plate incorporation	100-10,000 µg/plate	±S-9	-	Positive controls used with each strain	Zeiger et al., 1982
Clastogenic events	CHO cells	sodium salt of o-phthalic acid	liquid suspension	10-50 mM	none	-	Studied chromatid breaks, chromosome breaks, interchanges	Phillips et al., 1982

(Florin et al., 1980; Zeiger et al., 1982). Phillips et al. (1982) noted no deleterious effects of the sodium salt of o-phthalic acid on chromosomal morphology in cultured CHO cells. No studies of m-phthalic acid were found.

5.3. TERATOGENICITY

No reproduction studies of m-phthalic acid were available. A summary of the fetotoxic effects of oral administration of o- and p-phthalic acid is provided in Table 5-3. No teratogenic effects were found. As part of a more comprehensive bioassay, CIIT (1982) administered 0, 0.03, 0.125, 0.5, 2.0 or 5.0% dietary p-phthalic acid to groups of 10 male and 10 female adult Wistar and CD rats. After 90 days on this regimen, 10 breeding pairs/dietary level were established. The diets were maintained throughout mating, gestation, lactation and the postweaning period.

After 2 weeks of cohabitation, the breeding pairs were separated and the dams allowed to give birth. Parameters evaluated in the offspring were sex ratios, viability, survival, body weight, fertility index, litter size, clinical signs, morbidity and mortality. At weaning, all litters were culled to two males and two females and excess pups were sacrificed within 10 days for necropsy. The remaining pups were maintained on the same diet until day 51, when they were sacrificed. F_0 or F_1 rats dying at other times were also necropsied. Necropsies were primarily concerned with lesions in the thoracic and abdominal viscera, with special emphasis on the urinary system.

Among all treatment groups, there were 17 stillborn Wistar pups and 23 stillborn CD pups; the majority of the stillbirths, 13 Wistar pups and 22 CD pups, occurred in the 2 and 5% treatment groups. At 2%, 3/5 CD litters and 2/10 Wistar litters had stillborn pups. At 5%, 3/4 CD litters and 1/7 Wistar litters had stillborn pups. There were no stillborn control pups.

TABLE 5-3

Oral Teratogenicity Testing of Phthalic Acids

Phthalic Acid	Species/ Strain	No. of Dams at Start	Vehicle	Daily Dose	Treatment Days	Observation Days	Maternal Response	Fetal Response	Reference
p-	rat/Wistar	10/group	diet	2 or 5%	90 days before mating to post-weaning	days 1, 21 and 51 after birth	2/10 dead at 5%	Stillbirths, decrease in viability, weight loss in pups of dams; urinary tract lesions and stones at 5%; enlarged cecum	CIIT, 1982
p-	rat/CD	10/group	diet	2 or 5%	90 days before mating to post-weaning	days 1, 21 and 51 after birth	2/10 dead at 5% 1/10 dead at 2%	Same as above	CIIT, 1982
p-	rat/F344	4-7/group	diet	5%	gestation day 7 to weaning	days 5-45 after birth	NR	Increased incidences of bladder calculi in pups sacrificed post-natal days 25-45	Wolkowski-Tyl et al., 1982
p-	mouse/ C3H/He	NR	diet	0.5%	weaning to death (F_0 generation)	NR	no effects on estrus, growth of dams, reproductive indices	No effects on growth rate or rearing rate	Nagasawa and Fujimoto, 1973
o-	rabbit	NR	NR	149.5 mg/kg/day	gestation days 7-12	NR	NR	No teratogenic effects	Smith et al., 1965

NR = Not reported

The offspring of CD dams were particularly affected by treatment. Compared with controls, CD pups exposed perinatally to the 2% concentration showed nearly a 30% decrease in survival, and a 20-25% decrease in body weight on day 21.

Relative to controls, viability was reduced 50% in high concentration male Wistar pups on day 1 after birth. Over 50% of the male and female CD pups exposed to the high concentration failed to survive to day 21, compared with a death rate of 2-3% in controls. Survival of Wistar pups was not as adversely affected between days 1 and 21. Postweaning, 13 Wistar pups and 11 CD pups at the high concentration died, while none died at the lower levels. The body weights of both sexes of Wistar pups fed 5% p-phthalic acid were significantly ($p<0.05$) lower than control weights on day 1; by day 21, the pups of both strains fed the 5% concentration showed reduced weights. No gross teratogenic effects were observed in pups; however, standard skeletal and visceral evaluations were not performed. Therefore, no conclusions regarding the absence of terata can be made from this study.

The pooled necropsy data on all 21- to 51-day-old pups revealed the incidence of bladder disorders (including whitish and yellowish bladders, bladder and renal calculi and thickened bladder walls) to be 8/18 in male Wistar rats and 18/31 female Wistar rats exposed to 5% p-phthalic acid. In CD rats exposed to the high concentration, the incidences were 5/9 (males) and 9/13 (females). Despite a small sample size, urinary tract toxicity was more pronounced in those pups sacrificed at day 51 than in those dying earlier or sacrificed at weaning. At concentrations <5%, the incidence of calculi was negligible. The only other treatment-related effect seen grossly in high concentration pups was an enlarged cecum.

Wolkowski-Tyl et al. (1982) administered 0.5 or 5% dietary p-phthalic acid to five and six, respectively, gravid F344 rats. Administration began on gestation day 7 through parturition and weaning. A separate group of four dams received 5% p-phthalic acid from postnatal day 1 through weaning. Seven controls received a standard diet. After weaning pups were exposed to 0.5 or 5% dietary p-phthalic acid up to day 45 or sacrifice. Pups were sacrificed starting on postnatal day 5 and continuing every 5 days until day 45. At sacrifice, the kidneys, ureters, bladder and urethra were examined for calculi. No bladder stones were found in pups from any group at any sacrifice up to and including postnatal day 20. The bladder stone incidence was markedly increased, however, from days 25-45 in pups whose dams were exposed to the 5% diets, whether starting on gestation day 7 or on postnatal day 1. The incidence in the 5% group exposed starting on gestation day 7 was 39/52 (75%); the incidence in 5% group exposed starting on postnatal day 1 was 18/22 (81.8%). No bladder calculi were found in the controls or in the 0.5% group exposed starting on gestation day 1. The results indicate that despite the fact that p-phthalic acid passes to the fetus from the dam and is delivered in the milk, no calculi were found in neonatal rats until the animals had begun to self feed.

Nagasawa and Fujimoto (1973) mated male and female C3h/He mice after ~50 days of dietary administration of 0.5% p-phthalic acid. This regime was apparently continued throughout gestation and lactation. There were no effects on pup weight measured on postnatal days 0, 12 and 20 or growth rate.

A study by Smith et al. (1965) regarding the reproductive effects of oral o-phthalic acid in rabbits was described by Freese et al. (1979). Dams were orally dosed with 0.9 mmol/kg/day (149.5 mg/kg/day) from days 7-12 of gestation. No teratogenic effects were found.

Five Swiss mice dams were intraperitoneally injected with 200 or 400 mg/kg o-phthalic acid in a saline-Tween 20 vehicle on the 9th day of gestation (Koehler et al., 1971). There were no compound-related effects on indices of implantation or resorptions, relative to untreated controls. Phthalic acid exposure also did not lead to a single malformation in 118 live births.

5.4. OTHER REPRODUCTIVE EFFECTS

Male Sprague-Dawley rats, 3-4 weeks old, were orally administered ~2300 mg/kg/day of the sodium salt of o-phthalic acid in aqueous solution in a study designed to assess whether the metabolites of di-butyl phthalate exerted testicular effects in mammals (Cater et al., 1977). The length of treatment was 4-6 days. o-Phthalic acid had no effects on testicular tissues. Oishi and Hiraga (1980) fed diets containing 2% o-phthalic acid to 5-week-old male JCLi Wistar rats for 1 week. After treatment, the rats were sacrificed, and serum, testes, liver and kidneys were obtained, and tissue zinc concentration measured. Treatment had no effect on either organ weight or zinc concentrations.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Gross (1974) administered concentrations of 0, 1, 2 or 5% dietary p-phthalic acid to groups of 50 male and 50 female Wag/Rij rats for 2 years (see Section 5.1.). Rats were weighed periodically throughout the study, and histological analysis was performed on all rats that died or were killed when moribund or after 2 years unless precluded by autolysis. At sacrifice, blood was taken for routine hematological and blood urea concentration analyses.

In contrast to the findings in the control and lower two concentration groups, rats treated at the 5% concentration had a greatly accelerated mortality rate, which was different from control rates as early as 5 months after treatment began. Only 15 males and 16 females chronically fed 5% p-phthalic acid survived to the end of the study. After 24 months, body weights were significantly ($p<0.01$) depressed in the 5% females and the 2 and 5% males, compared with controls; however, there were no treatment-related effects at any concentration on hematological or bone marrow measures.

In females exposed to 1 or 2% p-phthalic acid, the relative weights of the liver, kidney and heart were significantly depressed. The absolute weights of these tissues were also depressed at these levels particularly in females. At the 5% concentration, rats of both sexes showed adrenal hypertrophy, and males had elevated relative weights of the kidneys and heart.

Gross (1974) predominantly noted bladder urolith formation and renal nephropathy in the groups treated with 5% p-phthalic acid; uroliths and nephropathy each occurred in 80-93% of the 34-47 rats examined. Bladder stones and nephropathy were observed in none of the 45-46 controls examined and in 0 or 1 of 43-50 rats in the groups treated at 1 and 2%. Kidneys of the high concentration rats showed variable degrees of damage, but typically manifested signs of chronic inflammation. These signs included pyelonephritis, perinephritis and papillar deposition of basophilic material, which probably represented precipitated p-phthalic acid. The number of rats with blood urea levels >40 mg % was significantly ($p<0.02$) elevated in high concentration males and females. Also pronounced in the high concentration groups was hyperplasia of the urinary epithelium, which was proposed to develop into benign papillomas and malignant tumors (see Section 5.1.).

In F344 rats of both sexes given dietary levels of p-phthalic acid equivalent to 0, 20, 142 or 1000 mg/kg/day for 2 years, no urinary tract calculi were noted in any rat sacrificed at interims of 6 or 12 months (CIIT, 1983). At 18 months, 2/27 high-dose females and at 24 months, 11/86 high-dose females had urinary tract calculi; no other rats sacrificed at 18 or 24 months exhibited this effect. At terminal sacrifice, only high concentration females had hyperplasia of the bladder urothelium. During the course of the study, however, the rats were exposed to constant illumination for an unknown period of time, and the influence of such illumination on the effects are unknown.

In a subchronic study in Charles River Wistar and CD rats, males and females were administered p-phthalic acid in the diet (CIIT, 1982). The rats were started on test at 15-17 weeks of age. Thirty rats/sex/strain were administered 0, 0.03, 0.125, 0.5, 2.0 or 5.0% p-phthalic acid in a randomized block design.

The groups of surviving rats were subjected to three interim and one final sacrifice. Within each block, a maximum of 5 rats were sacrificed on day 30, 5 on day 60 and 10 on day 90. Rats dying at other times were also necropsied. Ten breeding pairs were maintained for reproductive studies (see Section 5.3.). All adult rats were assessed for food consumption and body weights weekly. They were observed twice daily for clinical signs, evidences of morbidity and mortality, and were given weekly examinations. At sacrifice, urine samples were taken to determine pH, specific gravity, electrolyte content and p-phthalic acid excretion. Histological examinations were performed on major internal organs, with particular emphasis on kidneys and lower urinary tract structures. Microscopic study of the right kidney and ureter was also performed.

Female Wistar rats given 5.0% dietary p-phthalic acid and female CD rats given 2 or 5% dietary concentrations had statistically significant reductions in food consumption, relative to controls. All groups of rats fed 0.5-5.0% showed a concentration dependent decline in body weights. Average body weight gain was consistently statistically significantly lower in the 5.0% concentration groups and, at the 90-day sacrifice, significant inhibitions in weight gain were observed in both sexes of CD rats exposed to dietary concentrations of 0.5 and 2.0%. At the 5.0% concentration, weight loss, diarrhea and urogenital discharge were observed during the first 4 weeks. No deaths were recorded before day 35, but from days 35-90, three CD females, one Wistar female and one Wistar male from the 5.0% groups died.

With increases in exposure duration from 30-90 days, there was a tendency toward increased acidity in the urine, with significantly lower pHs after 90 days in rats exposed to concentrations of $\geq$0.5%. There were concentrated-related trends in the excretion of urinary calcium, magnesium and phosphate that were not statistically significant; however, the lack of statistical significance may have been a result of the small sample sizes used. In general, concentration-related increased excretion of urinary calcium was observed starting with the 0.5% level, and increased excretion of urinary magnesium was found in the 2 and 5% males of both strains, at the 90-day sacrifice. Elevated phosphate excretion was observed at the 5% dietary level in all groups. Urinary p-phthalic acid output was increased beginning with the 0.5% concentration level, particularly in Wistar rats. p-Phthalic acid administration did not alter kidney weights.

The most frequent gross observations upon necropsy were bladder distention, calculi in the bladder and distention of the cecum and colon. These effects occurred primarily in the 5% groups. All treatment groups had

hepatic nodules and parasitic cysts. Histopathological examination revealed little correlation between inflammatory lesions of the bladder and the presence of calculi. Low incidences of ureter lesions, chronic cystitis and urethritis at the high concentration precluded definitive conclusions. Calculi were found in 1/10 male Wistar rats sacrificed at 30 days, 4/10 male and 1/10 female Wistar rats at 90 days, 1/10 female CD rats exposed to the 5.0% concentration and 1/10 male Wistar rats exposed to the 0.03% concentration and sacrificed at 90 days. Bladder and ureteral transitional cell hyperplasia after 90 days was common in all groups exposed to the 5.0% concentration.

Vogin (1972) conducted a 90-day feeding study of p-phthalic acid in Wistar-derived male and female rats (~30 days old). The concentration used was 5% for 1 week, followed by 3% until termination. It was not clear whether a control was used. Upon sacrifice, 11/18 treated males and 3/19 treated females had bladder stones, and hyperplasia of the bladder urothelium was diagnosed in 13/18 males and 3/19 females. Of the 13 males with transitional cell hyperplasia, 8 had calculi; all 3 females with hyperplasia also had calculi. Thus, there was a strong correlation between the presence of calculi and the development of hyperplasia. All pathological changes occurred in the urinary tract.

The susceptibility of weanling rats to p-phthalic acid ingestion was studied by Chin et al. (1981). Groups of 30 weaned 28-day-old male and female F344 pups were exposed to dietary p-phthalic acid at concentrations of 0, 0.5, 1.5, 3, 4 or 5% for 14 days. Body weights and food and water consumption were measured on alternate days. Upon sacrifice on day 42, urine was collected, and the entire urinary tract examined for macroscopic calculi. Samples of bladder calculi were weighed and analyzed for minerals.

The body weights of pups exposed to 4 or 5% p-phthalic acid were significantly depressed. Pups given these levels also had a reduced food intake; however, pups exposed to 3, 4 and 5% p-phthalic acid had statistically significant elevated levels of water consumption and often were afflicted with diarrhea. The authors attributed these findings to the incomplete gastrointestinal absorption of p-phthalic acid (see Section 4.1.). At concentrations of 0, 0.5 or 1.5% p-phthalic acid, only one female (at 1.5%) had calculi. A concentration-related trend in calculi formation was apparent in both sexes exposed to dietary concentrations of 3-5%; at the 5% level, 28/30 males and 22/30 females were affected. Males showed a steeper trend than did females.

In addition to concentration-related decreases in urinary pH, there were also decreases in urinary sodium, potassium and sulfate. The calculi were found to be principally composed of calcium p-phthalate and calcium phosphate. Chin et al. (1981) performed histological examinations on the urinary tract of 10 male controls and 10 males exposed to the 4% concentration. In the controls and in four treated rats without calculi, histology of the urinary tract was essentially normal. In the six treated rats with bladder calculi, the thickened transitional epithelium was diffusely hyperplastic. In some instances, the transitional epithelium layer extended into the lamina propria and muscular wall. Ulceration of the epithelial surface and neutrophil infiltration of the lamina propria were often observed. In contrast, in five of these rats with calculi, the kidneys and ureters maintained normal cytoarchitecture, although one rat had hydronephrosis.

Pertinent data regarding the subchronic and chronic toxicity of o- and m-phthalic acid could not be located in the available literature as cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} value in rats for o-phthalic acid is 7900 mg/kg, for m-phthalic acid is 10,400 mg/kg and for p-phthalic acid is 18,800 mg/kg (NIOSH, 1985). Caujolle and Meynier (1958) reported intraperitoneal LD_{50}s in mice of 1670, 3700 and 4200 mg/kg for o-, p- and m-phthalic acids, respectively.

Hoshi et al. (1968) fed separate groups of Swiss albino mice 766-852 mg/kg/day p-phthalic acid (as a 0.5% dietary concentration) for 7 days for study of a variety of physiological and metabolic parameters. When administered by the oral route, the compound did not affect renal function (as measured by phenolsulfophthalein retention) but did accelerate the excretion of bromosulfophthalein. p-Phthalic acid had no effect on plasma transaminase levels or hepatocyte morphology, but did slightly decrease the barbiturate sleeping-time. Lake et al. (1974) showed that intragastric administration of 850 mg/kg/day of o-phthalic acid for 7 days to rats had no effect on liver weight, hepatic enzyme activity or cytochrome P-450 content.

Some studies reported that oral administration of p-phthalic acid prolongs the plasma half-life of tetracyclines in rabbits (Hoshi et al., 1967; Takagi et al., 1967) and rats (Hoshi et al., 1967); however, this effect was not found in either of these species in a study by Grigas et al. (1971). Since the design of the rat studies of Hoshi et al. (1967) and Grigas et al. (1971) were virtually identical, these discrepancies are inexplicable.

In vitro studies (Graves et al., 1967) have shown that both o-phthalic acid and thalidomide at a concentration of 0.1 M decrease bovine spermatozoa respiration by 50%. Freese et al. (1979) demonstrated that >15.0 mM o-phthalic acid inhibited the growth of a cultured human HeLa cell line, and >6.7 mM inhibited the growth of a *Bacillus subtilis* line. The authors

attributed the inhibition of bacterial cell duplication by lipophilic acids to inhibition of the active membrane transport of nutrients.

5.7. SUMMARY

In a 2-year study, male and female rats receiving 5% p-phthalic acid in the diet had significantly increased incidences of lesions in the bladder and ureter, which represented a progression ranging through hyperplasia, papilloma, squamous metaplasia to transitional cell tumors or squamous cell carcinoma (Gross, 1974). These lesions occurred at low incidences in rats given 1 or 2%, while none were observed in controls. Increased incidences of transitional cell adenomas and carcinomas were observed in female rats treated for 2 years with p-phthalic acid in the diet at an equivalent dose of 1000 mg/kg/day (CIIT, 1983). The incidence of adenomas was statistically significantly higher than controls. The incidence was not increased in 1000 mg/kg/day males nor in males or females at $\leq$142 mg/kg/day.

p-Phthalic acid was negative for reverse mutations in Salmonella typhimurium with and without metabolic activation (Florin et al., 1980; Zeiger et al., 1982). o-Phthalic acid was negative for chromosome damage in cultured CHO cells (Phillips et al., 1982).

Administration of 2 or 5% dietary p-phthalic acid to breeding pairs of Wistar and CD rats through postweaning, mating and gestation led to decreased viability of male Wistar pups 1 day after birth and of male and female CD pups 21 days after birth (CIIT, 1982). Stillbirths were most prevalent at these two dietary concentrations. Overall, however, neither fertility index nor litter size were adversely affected by treatment. After weaning, dams were continued on their respective diets, as were the pups until dead or sacrificed on day 51. Postweaning, all pups that died had

been exposed to the 5% dietary level. The high concentration pups also had urinary tract damage and bladder calculi. No treatment-related terata were noted.

Wolkowski-Tyl et al. (1982) presented evidence that rat pups that were born to dams fed 5% dietary p-phthalic acid during gestation and lactation or during lactation only did not develop uroliths by postnatal day 20. Rat pups that were exposed in utero or during nursing, however, developed high incidences of uroliths when they were continued on the 5% diet after weaning. In C3H/He mice perinatally exposed to 0.5% p-phthalic acid, there were no reported adverse effects in either the parental or the F_1 generation (Nagasawa and Fujimoto, 1973).

o-Phthalic acid was not teratogenic or fetotoxic to the offspring of rabbit dams treated orally at 149.5 mg/kg/day (Smith et al., 1965) or mouse dams injected intraperitoneally with up to 400 mg/kg during gestation (Kōhler et al., 1971). No testicular effects were observed in male rats treated by gavage with 2300 mg/kg o-phthalic acid (Cater et al., 1977) or in the diet at 2% for 1 week (Oishi and Hiraga, 1980).

Lifetime administration of 5% dietary p-phthalic acid to Wag/Rij rats led to a greatly accelerated mortality rate relative to controls, evident soon after the onset of treatment (Gross, 1974). Body weights were significantly depressed in females given the 2% concentration, and both relative and absolute liver, kidney and heart weights were decreased in rats receiving the 1 or 2% dietary levels. Increased incidences of uroliths and renal nephropathy were observed only in the rats treated at the 5% dietary concentration; at this level, virtually all rats exhibited urinary tract disorders. Also pronounced at the 5% concentration were nephritis, elevated blood urea levels and hyperplasia progressing to malignant neoplasia of the urinary epithelium.

Female F344 rats fed the dietary equivalent of 1000 mg/kg/day for 18-24 months showed a slight increase in bladder stone formation and transitional cell tumors; these effects were not observed in any rats at ≤142 mg/kg/day (CIIT, 1983).

The CIIT (1982) also conducted a subchronic study of dietary p-phthalic administration in Wistar and CD rats. Concentrations used were 0, 0.03, 0.125, 0.5, 2.0 and 5.0%. Rats were sacrificed after 30, 60 or 90 days on the diet, and most adverse effects occurred after the 90-day treatment. These effects, occurring principally in the 5.0% concentration rats, included bladder hyperplasia and distention, bladder calculi, distention of the cecum and colon, and mortality. Starting at the 0.5% level, there were concentration-related trends in urinary acidity, the excretion of urinary electrolytes and inhibition in body weight gain. Vogin (1972) observed urolith formation and urinary tract hyperplasia in young rats exposed to a TWA dietary concentration of 3.15% p-phthalic acid for 90 days.

Chin et al. (1981) further demonstrated the susceptibility of young rats to p-phthalic acid intoxication by orally administering the compound for 2 weeks to 28-day-old weanlings. At ≥3%, urolith formation was concentration-related, and upon gross necropsy, the affected rats also showed hyperplasia of the bladder and occasional hydronephrosis. The investigators found decreases in urinary sodium, potassium and sulfate in these rats. Microscopic analysis of the urinary tracts of male rats treated with a level of 4% revealed ulceration of the bladder epithelium, inflammation and hyperplasia.

The oral LD_{50}s of o-, m- and p-phthalic acid in rats are 7900, 10,400 and 18,800 mg/kg, respectively (NIOSH, 1985).

6. AQUATIC TOXICITY

6.1. ACUTE

Pertinent data regarding the acute toxicity of phthalic acid to fish or aquatic invertebrates could not be located in the available literature as cited in the Appendix. Nishiuchi (1980) reported that the 24-hour LC_{50} for the toad, Bufo bufo japonicus (life stage not reported), was 36-40 mg/ℓ.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of phthalic acid to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding effects of phthalic acid on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUE

Fathead minnows, Pimephales promelas, exposed to seven concentrations of [^{14}C]•di-2-ethylhexylphthalate ranging from 1.9-62 µg/ℓ for 56 days accumulated radioactivity to 200-800 times the concentration in the ambient water. Of the total radioactivity, ~5% was phthalic acid and 3-4% was glucuronide conjugates of phthalic acid (Mayer, 1976).

Channel catfish, Ictalurus punctatus, exposed to 1 µg/ℓ [^{14}C]-di-2-ethylhexyl phthalate for 24 hours accumulated total residues equivalent to 2.6 µg/g [^{14}C]-di-2-ethylhexyl phthalate. Of the residues, 4% were phthalic acid and 0.3% were conjugates of phthalic acid (Johnson et al., 1977).

6.5. SUMMARY

Little information is available concerning effects of phthalic acid on aquatic organisms. The only toxicity data found was an LC_{50} of 36-40 mg/ℓ for the frog, Bufo bufo japonicus (Nishiuchi, 1980). Studies with two fish species, fathead minnows and channel catfish, exposed to radiolabeled di-2-ethylhexyl phthalate indicated that ~5% of the total accumulated radioactivity was in the form of phthalic acid and its conjugates (Johnson et al., 1977; Mayer, 1976).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from phthalic acids could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

In a 2-year study, male and female rats receiving 5% p-phthalic acid in the diet had significantly increased incidences of lesions in the bladder and ureter, which represented a progression ranging through hyperplasia, papilloma, squamous metaplasia to transitional cell tumors or squamous cell carcinoma (Gross, 1974). These lesions occurred at low incidences in rats given 1 or 2%, while none were observed in controls. Increased incidences of transitional cell adenomas and carcinomas were observed in female rats treated for 2 years with p-phthalic acid in the diet at an equivalent dose of 1000 mg/kg/day, compared with controls (CIIT, 1983). The incidence was not increased in 1000 mg/kg/day males nor in males or females at $\leq$142 mg/kg/day.

p-Phthalic acid was negative for reverse mutation in Salmonella typhimurium with and without metabolic activation (Florin et al., 1980; Zeiger et al., 1982). o-Phthalic acid was negative for chromosome damage in cultured CHO cells (Phillips et al., 1982).

Administration of 2 or 5% dietary p-phthalic acid to breeding pairs of Wistar and CD rats through postweaning, mating and gestation led to decreased viability of male Wistar pups 1 day after birth and of male and female CD pups 21 days after birth (CIIT, 1982). Stillbirths were most prevalent at these two dietary concentrations. Overall, however, neither fertility index nor litter size was adversely affected by treatment. After weaning, dams were continued on their respective diets, as were the pups until dead or sacrificed on day 51. Postweaning, all pups that died had been exposed to the 5% dietary level. The high concentration pups also had urinary tract damage and bladder calculi.

Wolkowski-Tyl et al. (1982) presented evidence that rat pups born to dams and fed 5% dietary p-phthalic acid during gestation and lactation or during lactation only do not develop uroliths by postnatal day 20. Rat pups that were exposed in utero or during nursing, however, developed high incidences of uroliths when they were continued on the 5% diet after weaning. In C3H/He mice perinatally exposed to 0.5% p-phthalic acid, there were no reported adverse effects in either the parental or the F_1 generation (Nagasawa and Fujimoto, 1973). In chickens fed p-phthalic acid, Kono and Nakajima (1965) noted testicular interstitial cell damage.

o-Phthalic acid was not teratogenic or fetotoxic to the offspring of rabbit dams treated orally at 149.5 mg/kg/day (Smith et al., 1965) or mouse dams injected intraperitoneally with up to 400 mg/kg during gestation (Köhler et al., 1971). No testicular effects were observed in male rats treated by gavage with 2300 mg/kg o-phthalic acid (Cater et al. 1977) or in the diet at 2% for 1 week (Oishi and Hiraga, 1980).

Lifetime administration of 5% dietary p-phthalic acid to Wag/Rij rats led to a greatly accelerated mortality rate relative to controls, evident soon after the onset of treatment (Gross, 1974). Body weights were significantly depressed in females given the 2% concentration, and both relative and absolute liver, kidney and heart weights were decreased in rats receiving the 1 or 2% dietary levels. Increased incidences of uroliths and renal nephropathy were observed only in the rats treated at the 5% dietary concentration; at this level, virtually all rats exhibited urinary tract disorders. Also pronounced at the 5% concentration were nephritis, elevated blood urea levels and hyperplasia progressing to malignant neoplasia of the urinary epithelium.

Female F344 rats fed the dietary equivalent of 1000 mg/kg/day for 18-24 months showed a slight increase in bladder stone formation and transitional cell tumors; these effects were not observed in any rats at ≤142 mg/kg/day (CIIT, 1983).

The CIIT (1982) also conducted a subchronic study of dietary p-phthalic administration in Wistar and CD rats. Concentrations used were 0, 0.03, 0.125, 0.5, 2.0 and 5.0%. Rats were sacrificed after 30, 60 or 90 days on the diet, and most adverse effects occurred after the 90-day treatment. These effects, occurring principally in the 5.0% concentration rats, included bladder hyperplasia and distention, bladder calculi, distention of the cecum and colon, and mortality. Starting at the 0.5% level, there were concentration-related trends in urinary acidity, the excretion of urinary electrolytes and inhibition in body weight gain. Vogin (1972) observed urolith formation and urinary tract hyperplasia in young rats exposed to a TWA dietary concentration of 3.15% p-phthalic acid for 90 days.

Chin et al. (1981) further demonstrated the susceptibility of young rats to p-phthalic acid intoxication by orally administering the compound for 2 weeks to 28-day-old weanlings. At ≥3%, urolith formation was concentration-related, and upon gross necropsy, the affected rats also showed hyperplasia of the bladder and occasional hydronephrosis. The investigators found decreases in urinary sodium, potassium and sulfate in these rats. Microscopic analysis of the urinary tracts of male rats treated with a level of 4% revealed ulceration of the bladder epithelium, inflammation and hyperplasia.

There are insufficient data on o- or m-phthalic acid for quantitative risk assessment. Therefore, derivation of values for estimation of risk to human populations will only be done for p-phthalic acid.

The findings of Gross (1974) and CIIT (1983) indicate that the urinary system is the target for chronic exposure to phthalic acid. In the study by Gross (1974), rats treated at dietary levels of 1 or 2% (500 or 1000 mg/kg/day) had low, nonsignificant incidences of urinary calculi and histopathological lesions. In addition, relative and absolute kidney weights were significantly decreased compared with controls. Because high incidences of calculi and histopathological lesions were found in the urinary system at higher doses, the effect on kidney weight is considered adverse. Therefore, the LOAEL in the chronic studies is 500 mg/kg/day. The next lowest dose in the chronic studies is 142 mg/kg/day, at which no effects in rats were reported (CIIT, 1983). The NOEL of 142 mg/kg/day is well below those doses in subchronic or reproductive studies that result in adverse effects.

Exposure to p-phthalic acid resulted in significantly increased incidences of urinary tract cancer; however, the carcinogenic response may be secondary to the urolithic effects of p-phthalic acid, in which case the nonthreshold model will overestimate risk. Transitional cell adenomas and carcinomas of the bladder occurred in female rats treated with p-phthalic acid at a dietary level equivalent to 1000 mg/kg/day (CIIT, 1982). Although independent histological analysis by two separate laboratories revealed somewhat different incidences, the incidences of adenomas determined by either laboratory were statistically significantly higher than controls ($p \leq 0.005$) (see Section 5.1.). Carcinomas occurred in only one or two 1000 mg/kg/day females. Gross (1974) also provided evidence that a statistically significant neoplastic response to p-phthalic acid occurs after very high doses. Although the separate incidences of hyperplasia, benign tumors and malignant tumors were not reported, the incidence data represented a progression of changes ranging through hyperplasia, papilloma, squamous metaplasia to transitional cell tumors or squamous cell carcinomas.

The CIIT (1983) study may be used for risk assessment, however, there were several deficiencies or technical problems with this study. Deficiencies of this study include a high incidence of eye lesions and uterine cancer in all dose groups and technical difficulties with the photoperiod. These factors may be balanced by a more accurate measure of dose, more detailed reporting of lesions and larger group sizes than the Gross (1974) study. Female rats, but not males, showed an increased incidence of transitional cell adenomas in the high-dose (1000 mg/kg) group at the terminal sacrifice. Low- and mid-dose animals were not evaluated initially, but a subsequent reading of these slides by a different group did not indicate that tumors were found. Three slides from the high-dose group initially read as positive were the subject of contention following a second reading by an independent group. Unfortunately, the second evaluation appeared to be based on an incomplete set of slides. Furthermore, given the postulated relationship between urolithiasis and tumor presence, and considering the lack of response of any type associated with doses of $\leq$500 mg/kg/day, it is not advisable to estimate the risk of cancer for low doses of p-phthalic acid using the available data and the multistage model.

Therefore, using the findings of Gross (1974) and CIIT (1983), an RfD for p-phthalic acid of 1.4 mg/kg/day (98 mg/day) was derived by dividing the NOEL of 142 mg/kg/day by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect sensitive subgroups in the human population).

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The toxicity from chronic and subchronic dietary p-phthalic acid was described in Chapter 5 and is summarized in Table 9-1.

RQ derivations are provided in Table 9-2. The most severe effect cited by Gross (1974) in rats administered 5% p-phthalic acid was an accelerated rate of mortality. This effect was also reported by CIIT (1982) in rats given a concentration of 5% (3084 mg/kg/day) and in a 1-generation reproductive study in CD rat dams administered 2 or 5% concentrations; however, in the reproductive study, the incidence data were too low to draw firm conclusions, and in similarly treated Wistar dams mortality was not concentration-related.

It is, therefore, appropriate to score the Gross (1974) results for mortality. A lifetime dietary concentration of 50,000 ppm corresponds to 2500 mg/kg/day (U.S. EPA, 1980b). Multiplication of this value by the cube root of the ratio of the rat body weight (0.35 kg) to the reference human body weight (70 kg), and by 70 kg to convert to mg/day, leads to a chronic human MED of 29,925 mg/day. The MED corresponds to an RV_d of 1. As an increased rate of mortality merits an RV_e of 10, the CS is 10, and the RQ is 1000.

After a dietary concentration of 2% p-phthalic acid, Wistar and especially CD rat dams had increased numbers of stillborn pups relative to controls (CIIT, 1982) (see Table 9-1). Postparturition, the survival of treated CD pups was markedly decreased, and surviving pups were unable to maintain body weight comparable with controls. These effects warrant an RV_e of 10. The concentration used corresponds to an equivalent rat dose of 1000 mg/kg/day. Multiplying by the cube root of the body weight ratio

TABLE 9-1

Oral Toxicity Summary for p-Phthalic Acid

Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Rat/Wag/R1j	M,F	50M & 50F per group	0.35[a]	diet	97.3%	5% for 104 weeks	2500[b]	Accelerated mortality, adrenal hypertrophy, urolith formation, renal nephropathy and necrosis, chronic inflammation, elevated blood urea, urinary tract hyperplasia	Gross, 1974
Rat/Wag/R1j	M,F	50M & 50F per group	0.35[a]	diet	97.3%	2% for 104 weeks	1000[b]	Decreased relative and absolute weights of liver, kidney and heart (females); reduced body weight gain (males)	Gross, 1974
Rat/Wag/R1j	M,F	50M & 50F per group	0.35[a]	diet	97.3%	1% for 104 weeks	500[b]	Decreased relative and absolute kidney and liver weight (females) decreased relative kidney weight (males)	Gross, 1974
Rat/F344	M,F	NR	0.35[a]	diet	NR	1000 mg/kg/day for 104 weeks	1000	Slightly elevated incidences of uroliths and urinary tract hyperplasia	CIIT, 1983
Rat/Wistar	M,F	30M & 30F per group	0.481 (M) 0.278 (F)[c]	diet	NR	5% for 30, 60 or 90 days	2480 (M), 3018 (F)[d]	Decreased body weight gain; increased urinary acidity and electrolytes; bladder, colon, cecum distension; hyperplasia; bladder calculi (males)	CIIT, 1982
Rat/Wistar	M,F	30M & 30F per group	0.506 (M) 0.291 (F)[c]	diet	NR	2% for 30, 60 or 90 days	960 (M), 1219 (F)[d]	Decreased body weight gain, increased acidity and electrolyte excretion in urine, distention of cecum and colon (males)	CIIT, 1982
Rat/Wistar	M,F	30M & 30F per group	0.499 (M) 0.286 (F)[c]	diet	NR	0.5% for 30, 60 or 90 days	249 (M), 307 (F)[d]	Increased urinary acidity and calcium excretion	CIIT, 1982
Rat/CD	M,F	30M & 30F per group	0.487 (M) 0.315 (F)[c]	diet	NR	5% for 30, 60 or 90 days	2499 (M), 2783 (F)[d]	Increased mortality (females), increased urinary acidity and electrolyte excretion, urinary tract hyperplasia, distention of cecum and colon, decreased body weight gain	CIIT, 1982
Rat/CD	M,F	30M & 30F per group	0.514 (M) 0.338 (F)[c]	diet	NR	2% for 30, 60 or 90 days	930 (M), 1107 (F)[d]	Increased urinary acidity; increased electrolyte excretion (males); distention of cecum and colon; decreased body weight gain	CIIT, 1982

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TABLE 9-1 (cont.)

Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Rat/CD	M,F	30M & 30F per group	0.508 (M) 0.336 (F)[c]	diet	NR	0.5% for 30, 60 or 90 days	269 (M), 319 (F)[d]	Increased urinary acidity and calcium excretion, decreased body weight gain	CIIT, 1982
Rat/Wistar	M,F	NR	0.35[a]	diet	NR	5% for 1 week; 3% for 12 weeks TWA = 1.35%	1575[b]	Uroliths; urinary tract hyperplasia	Vogin, 1972
Rat/CD or Wistar	F	10 dams/ group	0.35[a]	diet	NR	5% in diet 90 days before mating to post-weaning	2500[b]	Stillbirths, decrease in pup survival and viability, loss of pup body weight, urinary tract lesions and stones, enlarged cecum, 2/10 maternal deaths	CIIT, 1982
Rat/CD or Wistar	F	10 dams/ group	0.35[a]	diet	NR	2% in diet 90 days before mating to post-weaning	1000[b]	Stillbirths, decrease in pup survival, loss of pup body weight, lactation deficits, 1/10 maternal deaths	CIIT, 1982

[a]Reference body weight (U.S. EPA, 1980b)

[b]Calculated assuming a rat eats a daily amount of food equal to 5% its body weight

[c]The average of the 30-day mean body weights provided by CIIT (1982)

[d]Calculated from total compound consumption/rat and the average of the 30-day mean body weights provided by CIIT (1982)

NR = Not reported

TABLE 9-2

Composite Scores for p-Phthalic Acid in the Rat*

Transformed Dose (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
2500	29,925	1	Increased mortality	10	10	1000	Gross, 1974
1000	11,970	1	Fetotoxicity: stillbirths, decreased survival	10	10	1000	CIIT, 1982

*Administered by the oral (diet) route

and by 70 kg results in a human MED of 11,970 mg/day, which corresponds to an RV_d of 1. Multiplication of the RV_d by the RV_e yields a CS of 10 which corresponds to an RQ of 1000.

Since exposure to $\geq$1000 mg/kg/day (Gross, 1974; CIIT, 1983; Vogin, 1972) produces effects with RV_es <10, it is not necessary to calculate CSs for these effects. Effects such as decreased relative organ weights, decreased body weight gain and increased excretion of calcium were observed at doses <1000 mg/kg/day; however, none of the doses were sufficiently low to result in MEDs that would correspond to an RV_d >1. Therefore, it is not necessary to calculate CSs for these effects. As shown in Table 9-3, the recommended RQ is 1000, based upon the data from CIIT (1982).

In a previous determination of the RQ for p-phthalic acid, U.S. EPA (1985c) used the same data as the basis. The study cited as Ledoux et al. (1982) in that document, however, is the same as the CIIT (1982) study cited in the present document.

Data are insufficient for deriving RQs for o- and m-phthalic acid (Table 9-4).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The results of a 2-year bioassay in rats conducted by Gross (1974) are described in Section 5.1. and Table 5-1. The high dietary concentration (5%) significantly accelerated mortality, as more than half of the rats of both sexes died by the end of the study. Of those high concentration rats examined histologically, ~60% had bladder or ureteral lesions that represented a progression ranging through hyperplasia, papilloma, squamous metaplasia to transitional cell tumors and squamous cell carcinomas. No control rats and few rats given either 1 or 2% dietary concentrations were found to have these lesions. The incidence of these neoplasms in the 5%

TABLE 9-3

p-Phthalic Acid

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	11,970 mg/day
Effect:	decreased survival of offspring
Reference:	CIIT, 1982
RV_d:	1
RV_e:	10
Composite Score:	10
RQ:	1000

*Equivalent human dose

TABLE 9-4

o- and m-Phthalic Acid

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ

dietary groups was statistically significant by both the Fisher Exact test ($p<0.001$) and the Cochran-Armitage test for dose-related trend ($p<0.001$). The high-dose rats also had very high incidences of bladder stones, which probably through irritation of the epithelium, promoted the neoplastic response. There were no increased incidences of other tumor types.

The CIIT (1983) conducted a 2-year bioassay of p-phthalic acid in F344 rats of both sexes. The rats received dietary levels equivalent to doses of 0, 20, 142 or 1000 mg/kg/day, and were sacrificed for tissue pathology at 6, 12, 18 or 24 months. At the 24-month sacrifice, the CIIT (1983) found increased incidences of transitional cell adenomas and carcinomas only in females exposed to the high concentration. Histological analyses were performed independently by two laboratories. One laboratory found transitional cell adenomas in 15/79 treated and 1/83 control rats and transitional cell carcinomas in 2/79 treated and 0/83 control rats. The other laboratory reported transitional cell adenomas in 10/73 treated and 1/71 control rats and carcinomas in 1/73 treated and 0/71 control rats. Fisher exact tests revealed that the incidences of adenomas determined by both laboratories were significantly greater than control ($p\leq0.005$).

Using the EPA Guidelines for Carcinogen Risk Assessment, based on the lack of epidemiologic and animal bioassay information, both m-phthalic acid and o-phthalic acid are classified as Group D (not classifiable as to human carcinogenicity). Using these Guidelines p-phthalic acid, based on the appearance of bladder tumors in male and female Wag/rij (Wistar) rats (Gross, 1974) and in female F344 rats (CIIT, 1983), might be classified as a B2 agent. The Guidelines, however, provide special comment when considering bladder tumors. In the two bioassays on p-phthalic acid the appearance of a significant increase in bladder tumors, occurring at only the highest doses,

2500 mg/kg/day in the Wistar rats and 1000 mg/kg/day in the female F344 rat, was associated with the presence of bladder stones (urolithiasis). The formation of stones was noted in subchronic studies as well. Since additional tissue damage not necessarily of a neoplastic nature occurred in the urinary tract suggesting that a maximum tolerated dose had been exceeded and since there was no indication of mutagenic potential, it seems appropriate to downgrade the classification of p-phthalic acid to a Group C agent. Furthermore, given the postulated relationship between urolithiasis and tumor presence, and considering the lack of response of any type associated with doses of $\leq$500 mg/kg/day, it is not advisable to estimate the risk of cancer for low doses of p-phthalic acid using the available data and the multistage model.

Phthalic acid

10. REFERENCES

Aftring, R.P., B.E. Chalker and B.F. Taylor. 1981. Degradation of phthalic acids by dentrifying mixed cultures of bacteria. Appl. Environ. Microbiol. 41: 1177-1183.

Bemis, A.G., J.A. Dindorf, B. Horwood and C. Samans. 1982. Phthalic acids, and other benzenepolycarboxylic acids. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 17, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, New York. p. 732-777.

Cater, B.R., M.W. Cook, S.D. Gangolli and P. Grasso. 1977. Studies on dibutyl phthalate-induced testicular atrophy in the rat: Effect on zinc metabolism. Toxicol. Appl. Pharmacol. 41(3): 609-618.

Caujolle, F. and D. Meynier. 1958. The toxicity of phthalic acids. Comp. Res. 246, 851. (Cited in Howard and Durkin, 1973)

Chin, T.Y., R.W. Tyl, J.A. Popp and H.D. Heck. 1981. Chemical urolithiasis. 1. Characteristics of bladder stone induction by terephthalic acid and dimethyl terephthalate in weanling Fischer-344 rats. Toxicol. Appl. Pharmacol. 58(2): 307-321.

CIIT (Chemical Industry Institute of Technology). 1982. A ninety-day study of terephthalic acid-induced urolithiasis and reproductive performance in Wistar and CD rats. CIIT, Research Triangle Park, NC.

CIIT (Chemical Industry Institute of Technology). 1983. Chronic dietary administration of terephthalic acid. CIIT, Research Triangle Park, NC.

CMR (Chemical Marketing Reporter). 1983. Chemical Profile: DMT-PTA. August 8, 1983.

Dorfman, L.M. and G.E. Adams. 1973. Reactivity of the hydroxyl radical in aqueous solution. NSRD-NBS-46. National Bureau of Standards, Washington, DC. 51 p. NTIS-COM-73-50623.

Dorney, J.R., J.B. Weber, M.R. Overcash and H.J. Strek. 1985. Plant uptake and soil retention of phthalic acid applied to Norfolk sandy loam. J. Agric. Food Chem. 33(3): 398-403.

Eaton, R.W. and D.W. Ribbons. 1982. Metabolism of dibutylphthalate and phthalate by Micrococcus sp. strain 12B. J. Bacteriol. 151: 48-57.

Engelhardt, G. and P.R. Wallnofer. 1978. Metabolism of di- and mono-n-butyl phthalate by soil bacteria. Appl. Environ. Microbiol. 35: 243-246.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 15(3): 219-232.

Foissy, E. 1979. Requirements in the taste neutrality of packaging. Milchwirtsch. Ber. Bundesanst. Wolfpassing Rotholz. 59: 105-110. (CA 92:20695h)

Freese, E., B.C. Levin, R. Pearce, et al. 1979. Correlation between the growth inhibitory effects, partition coefficients and teratogenic effects of lipophilic acids. Teratology. 20(3): 413-439.

Gerike, P. and W.K. Fischer. 1979. A correlation study of biodegradability determinations with various chemicals in various tests. Ecotoxicol. Environ. Saf. 3(2): 159-173.

Gerike, P. and W.K. Fischer. 1981. A correlation study of biodegradability determinations with various chemicals in various tests. II. Additional results and conclusions. Ecotoxicol. Environ. Saf. 5: 45-55.

Graves, C.N., G.W. Salisbury and J.R. Lodge. 1967. Mammalian spermatozoan metabolism in the presence of thalidomide. J. Anim. Sci. 26: 1082-0186.

Grigas, E.O., R. Ruiz and D.M. Aviado. 1971. Cardiopulmonary effects of antimalarial drugs. IV. Terephthalic acid and its dihydroxamic derivative (WR 74, 106). Toxicol. Appl. Pharmacol. 18(2): 469-486.

Gross, J. 1974. The effects of prolonged feeding of terephthalic acid (TPA) to rats. Project FG-IS-175. Agricultural Research Service, U.S. Department of Agriculture, Washington, DC.

Hansch, C. and A.J. Leo. 1985. MedChem Project Issue #26, Pomona College, Claremont, CA.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., New York. p. 581, 813, 999, 1000.

Heck, H.D. and R.W. Tyl. 1985. The induction of bladder stones by terephthalic acid, dimethyl terephthalate and melamine (2,4,6-triamino-s-triazine) and its relevance to risk assessment. Reg. Toxicol. Pharmacol. 5(3): 294-313.

Heukelekian, H. and M.C. Rand. 1955. Biochemical oxygen demand of pure organic compounds. J. Water Pollut. Control Assoc. 29: 1040-1053.

Hine, J. and P.K. Mookerjee. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J. Org. Chem. 40: 292-298.

Horowitz, A., D.R. Shelton, C.P. Cornell and J.M. Tiedje. 1982. Anaerobic degradation of aromatic compounds in sediment and digested sludge. Dev. Ind. Microbiol. 23: 435-444.

Hoshi, A. and K. Kuretani. 1967. Metabolism of terephthalic acid. III. Absorption of terephthalic acid from the gastrointestinal tract and detection of its metabolites. Chem. Pharm. Bull. 15(12): 1979-1984.

Hoshi, A. and K. Kuretani. 1968. Distribution of terephthalic acid in tissues. Chem. Pharm. Bull. 16(1): 131-135.

Hoshi, A., R. Yanai and K. Kuretani. 1967. Effect of terephthalic acid upon sulfadimethoxine contents in blood plasma. Chem. Pharm. Bull. 15(8): 1138-1144.

Hoshi, A., R. Yanai and K. Kuretani. 1968. Toxicity of terephthalic acid. Chem. Pharm. Bull. 16(9): 1655-1660.

Howard, P.H. and P.R. Durkin. 1973. Preliminary environmental hazard assessment of chlorinated naphthalenes, silicones, fluorocarbons, benzene-polycarboxylates, and chlorophenols. EPA 560/2-74-001. NTIS PB-238 074. 263 p.

Howe, R.B. and K.S. Crump. 1982. Global 82. A computer program to extrapolate quantal animal toxicity data to low doses. Prepared for Office of Carcinogen Standards, OSHA, U.S. Dept. of Labor under Contract No. 41USC252C3.

Inman, J.C., S.D. Strachan, L.E. Sommers and D.W. Nelson. 1984. The decomposition of phthalate esters in soil. J. Environ. Sci. Health. B19: 245-257.

Jaber, H.M., W.R. Mabey, A.T. Liu, T.W. Chou and H.L. Johnson. 1984. Data aquisition for environmental transport and fate screening for compounds of interest to the office of solid waste. EPA-600/6-84-010. NTIS PB84-243906.

Johnson, B.T., D.L. Stalling, J.W. Hogan and R.A. Schoettger. 1977. Dynamics of phthalic acid esters in aquatic organisms. In: Fate of Pollutants in the Air and Water Environments. Part 2. Chemical and Biological Fate of Pollutants in the Environment, I.H. Suffet, Ed. John Wiley and Sons, Inc., New York. p. 283-299.

Karasek, F.W. and S.H. Kim. 1975. Identification of the isomeric phthalic acids by mobility and mass spectra. Anal. Chem. 47(7): 1166-1168.

Kawamura, K., S. Steinberg and I.R. Kaplan. 1985. Capillary GC determination of short-chain dicarboxylic acids in rain, fog, and mist. Int. J. Environ. Anal. Chem. 19(3): 175-188.

Kawasaki, M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxic. Environ. Saf. 4: 444-454.

Kitano, M. 1978. Biodegradation and bioaccumulation test on chemical substances. OECD Tokyo Meeting. Reference Book TSU-No. 3.

Köhler, F., W. Meise and H. Ockenfels. 1971. Teratogenicity of thalidomide metabolites. Experientia. 27: 1149-1150.

Kono, K. and E. Nakajima. 1965. Effect of terephthalic acid on the viscera of chickens. II. Testis, thyroid, and anterior pituitary. Nippon Kakin Gakkaishi. 2: 205-219. (CA 66:44562b)

Lake, B.G., S.D. Gangolli, M.G. Wright, P. Grasso and A.G. Lloyd. 1974. Effects of the oral administration of bis(2-ethylhexyl) phthalate on hepatic enzymes in the rat. Biochem. Soc. Trans. 2(2): 322-325.

Ledoux, T.A., J.R. Reel and E.J. Gralla. 1982. A 90-day study of terephthalic acid induced urolithiosis and reproductive performance in Wistar and C5 rats. Final Report FYI-OTS-0482-0190. U.S. EPA, OTS, Washington, DC. (Cited in U.S. EPA, 1985c)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., New York. p. 5-6, 15-11, 15-16.

Matsumoto, G. 1982. Comparative study on organic constituents in polluted and unpolluted inland aquatic environments: 3. Phenols and aromatic acids in polluted and unpolluted waters. Water Res. 16(5): 551-558.

Matsumoto, G. and T. Hanya. 1980. Organic constituents in atmospheric fallout in the Tokyo area. Atmos. Environ. 14(12): 1409-1419.

Mayer, F.L. 1976. Residue dynamics of di-2-ethylhexyl phthalate in fathead minnows, Pimephales promelas. J. Fish. Res. Board Can. 33: 2610-2613.

Nagasawa, H. and M. Fujimoto. 1973. Inhibition by terephthalic acid of spontaneous tumorigenesis in mice. Experientia. 29(1): 89-90.

NIOSH (National Institute for Occupational Safety and Health). 1985. RTECS (Registry of Toxic Effects of Chemical Substances). On-line: October and December, 1985.

Nishiuchi, Y. 1980. Toxicity of formulated pesticides to freshwater organisms. Suisan Zoshoku. 28(2): 107-112. (Taken from SPHERE, 1985)

Oishi, S. and K. Hiraga. 1980. Testicular atrophy induced by phthalic acid esters: Effect on testosterone and zinc concentrations. Toxicol. Appl. Pharmacol. 53(1): 35-41.

Peakall, D.B. 1975. Phthalate esters: Occurrence and biological effects. Res. Rev. 54: 1-41.

Perry, J.J. and H.W. Scheld. 1968. Oxidation of hydrocarbons by microorganisms isolated from soil. Can. J. Microbiol. 14: 403-407.

Phillips, B.J., T.E.B. James and S.D. Gangolli. 1982. Genotoxicity studies of di(2-ethylhexyl)phthalate and its metabolites in CHO cells. Mutat. Res. 102(3): 297-304.

Pitter, P. 1976. Determination of biological degradability of organic substances. Water Res. 10(3): 231-235.

Ransley, D.L. 1984. Xylenes and ethylbenzene. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 24, 3rd ed. John Wiley and Sons, Inc., New York. p. 737, 740.

Ribbons, D.W. and W.C. Evans. 1960. Oxidative metabolism of phthalic acid by soil Pseudomonads. Biochem. J. 76: 310-318.

Sabljic, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Sadtler. n.d. Sadtler Standard Spectra. Sadtler Research Lab., Philadelphia, PA.

Saeger, V.W. and E.S. Tucker. 1973. Biodegradation of phthalate esters. Tech. Pap. Reg. Tech. Conf., Soc. Plast. Eng., Palisades Sect. p. 105-113.

Saeger, V.W. and E.S. Tucker. 1976. Biodegradation of phthalic acid esters in river water and activated sludge. Appl. Environ. Microbiol. 31(1): 29-34.

Sanbron, J.R., R.L. Metcalf, C. Yu and P. Lu. 1975. Plasticizers in the environment. Fate of di-n-octyl phthalate (DOP) in two model ecosystems and uptake and metabolism of DOP by aquatic organisms. Arch. Environ. Contam. Toxicol. 3(2): 244-255.

Sasaki, S. 1978. The scientific aspects of the chemical substance control law in Japan. In: Aquatic Pollutants: Transformation and Biological Effects, O. Hutzinger, L.H. Von Letyoeld and B.C.J. Zoeteman, Ed. Pergamon Press, Oxford. p. 283-298.

Shelton, D.R. and J.M. Tiedje. 1984. General method for determining anaerobic biodegradation potential. Appl. Environ. Microbiol. 47: 850-857.

Smith, R.L., S. Fabio, H. Schumaker and R.T. Williams. 1965. Studies on the relationship between the chemical structure and embryotoxic activity of thalidomide and related compounds. In: Embryopathic Activity of Drugs, J.M. Robson, F.M. Sullivan and R.L. Smith, Ed. J. and A. Churchill, London. (Cited in Freese et al., 1979)

Speece, R.E. 1983. Anaerobic biotechnology for industrial wastewater treatment. Environ. Sci. Technol. 17: 416A-427A.

SPHERE (Scientific Parameters for Health and the Environment, Retrieval and Estimation). 1985. AQUIRE database. Online: October 1985. U.S. EPA, OTS, Washington, DC.

SRI (Stanford Research Institute). 1985. 1984 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 540, 657, 783, 784, 926.

Takagi, K., T. Suzuki and Y. Saitoh. 1967. Effect of terephthalic acid on the blood levels of sulfaethylthiadiazole. Chem. Pharm. Bull. 15(10): 1597-1603.

Taylor, B.F. and D.W. Ribbons. 1983. Bacterial decarboxylation of o-phthalic acids. Appl. Environ. Microbiol. 46(6): 1276-1281.

Towle, P.H., R.H. Baldwin and D.H. Meyer. 1968. Phthalic acids. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 15, 2nd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 444.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Interim report to Congress. June, 1975. Washington, DC. EPA 600/D-75-001. NTIS PB 244-415/6BA.

U.S. EPA. 1980a. Phthalic Acid: Hazard Profile. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. ECAO, OHEA, ORD. U.S. EPA, Cincinnati, OH. [Also Published in Federal Register. 45(231): 79347-79357.]

U.S. EPA. 1984. Proposed Guidelines for Carcinogen Risk Assessment. Federal Register. 49(227): 46294-46301. CAG, U.S. EPA, Washington, DC.

U.S. EPA. 1985a. Fate of Atmospheric Pollutants (FAP). Computer Printout: Graphic Exposure Modelling System (GEMS). U.S. EPA, Office of Toxic Substances, Washington, DC.

U.S. EPA. 1985b. STORET Water Quality Data Base. Online: November 1985.

U.S. EPA. 1985c. Reportable Quantity Document for Terephthalic Acid. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S Production and Sales, 1984. USITC Publ. 1985. p. 25.

Vick, R.D., G.A. Junk, M.J. Avery, J.J. Richard and H.J. Svec. 1978. Organic emissions from combustion of combination coal refuse to produce electricity. Chemosphere. 7(11): 893-902.

Vogin, E.E. 1972. Subacute feeding studies (13-week) in rats with dimethylterephthalate (DMT), isophthalic acid (IA), and terephthalic acid (TA). Food and Drug Research Laboratories, Maspeth, NY. (Cited in Heck and Tyl, 1985)

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor Pressure Distribution of Selected Organic Chemicals. ORD, U.S. EPA, Cincinnati, OH. EPA 600/2-81-021.

Williams, D.T. and B.J. Blanchfield. 1974. Retention, excretion, and metabolism of phthalic acid administered orally to the rat. Bull. Environ. Contam. Toxicol. 12: 109-112.

Wolkowski-Tyl, R., T.Y. Chin and H.D. Heck. 1982. Chemical urolithiasis. III. Pharmacokinetics and transplacental transport of terephthalic acid in Fischer-344 rats. Drug Metab. Disp. 10(5): 486-490.

Wylie, G.D., J.J. Jones and B.T. Johnson. 1982. Evaluation of the river die-away biodegradation test. J. Water Pollut. Control Fed. 54(8): 1231-1236.

Zahn, R. and H. Wellens. 1980. Examination of biological degradability through the batch method -- Further experience and new possibilities of usage. Z. Wasser Abwasser Forsch. 13: 1-7.

Zeiger, E., S. Haworth, W. Speck and K. Mortelmans. 1982. Phthalate ester testing in the National Toxicology Program's Environmental Mutagenesis Test Development Program. Environ. Health Perspect. 45: 99-101.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following documents were obtained and reviewed in the preparation of this HEEP:

U.S. EPA. 1984. Health and Environmental Effects Profile for Terephthalic Acid. Final draft. ECAO-CIN-P055. ORD, ECAO, U.S. EPA Cincinnati, OH.

U.S. EPA. 1982. Chemical Hazard Information Profile. Terephthalic acid. Draft Report. OTS, OPTS, U.S. EPA, Washington, DC.